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BRAIN AND HEART

GIULIO FANO

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BRAIN AND HEART

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BRAIN AND HEART

Lectures on Physiology

BY

GIULIO FANO

OF THE ROYAL UNIVERSITY OF ROME

TRANSLATED BY

HELEN INGLEBY

WITH A FOREWORD BY

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TRANSLATOR'S NOTE

IN translating these lectures I have been at pains to render the author's thought accurately while endeavouring not to lose the spirit of the original. In the strictly scientific portions of the book the translation was kept as literal as possible to avoid the slightest deviation from the author's meaning. Elsewhere, when an exact rendering of the Italian into English could not be made, the English equivalent was given in other words.

I owe an important debt to Dr. Corrado Da Fano, who kindly revised the text with me and made many suggestions and improvements.

HELEN INGLEBY.

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PREFACE

THIS small volume is a collection of lectures given by invitation of the "Mancomunitat" of Barcelona and of the "Facolta medica" of Madrid, and I wish to express to those eminent colleagues and friends my appreciation of their cordial hospitality.

The lectures formed the material for a short course given before students who expressed a desire to know something of my investigations and scientific views. I have tried to satisfy their flattering request by giving an almost autobiographical character to my lectures. I have dwelt on some periods of my life as a physiologist, trusting they may be of interest, not merely for the theories advanced, but also for the demonstration of the logical sequence of ideas which has influenced the development and interpretation of my experiments.

Let it not be forgotten that, even in the most objective research, the investigator cannot alienate his temperament, and this is especially true of researches on the complicated, changeable, and often controversial processes that occur in living beings. In the attempts made to reveal the finer motor mechanism of organisms, which, like him, move and feel, the biologist almost irresistibly identifies himself with them, and on them projects his own peculiar sensibility, his intellectual idiosyncrasy, and the predominant motives of his conscious acts.

I have quoted the earliest of my works, for in spite of their age and frequent revision, they retain a certain

vigour which makes them worthy denizens of the scientific world. Further, I have dwelt mainly on certain functions of the brain and heart, because they lend themselves in a particular manner to general application. I have endeavoured not to limit myself to recording the results of researches, whether mine or of others; I have co-ordinated them and deduced certain theories from them, though realising full well that these will only be of ephemeral value. Theories, it must be remembered, are like scaffolding, temporarily erected for the construction of a building and taken down when done with. But should we for that reason despise their use in erecting the edifice and putting together the materials for its construction? Hypotheses, indeed, give an aim to scientific research, liable otherwise to remain fragmentary and disconnected. Few proofs have so far been accepted in support of the transformist theory explaining the origin of species. Yet the doctrine itself has had the immense merit of furnishing an ideal to morphology which had previously been but a dull collection of descriptions and classifications.

Let us not therefore ape those who would rid science of all speculation. Without conjecture, research becomes a form of empiricism leaving its creative powers to the sport of chance as pollen is diffused by the blind action of the winds. How much valuable seed thus goes astray! At the same time, let us not exaggerate the importance of theories and attribute to the temporary framework of a working hypothesis the solidity of a building capable of defying the corrosive action of time. Let us not forget that scientific research supplies increasingly effective means of conquering the forces of nature and adapting them to our needs, both racial and individual, making us at the same time unmistakably aware of our ignorance. Every day, it is true, we make headway along the uphill path of knowledge, but as we climb, the horizon recedes, unfolding an ever vaster expanse of problems unsolved. Thus science is the outcome of methods and ideas gathered in

the pursuit of truth rather than a heritage of strictly defined axioms.

The goal may never be attained, but, by striving towards it, our power to subdue the forces of nature is enhanced. Science, then, is a source of power rather than a fountain of knowledge. It leaves us free to explore the realm of the mind, to satisfy that inner impulse which urges us to shake the torch of creative thought in the dense night enveloping our existence, our origin, and our fate. The light is but a flicker, yet it stands for the highest power in human nature, it confers upon man a spark of the Divine.

GIULIO FANO.

January, 1926.

FOREWORD TO THE ENGLISH EDITION

THE author states in his preface that this book is the outcome of an invitation which he received to give a series of Lectures in the Universities of Barcelona and Madrid. It is not to be taken as a monograph dealing simply with the organs—heart and brain—which figure in the title, but as an outlook over wide questions of Physiology from the vantage-ground gained by him from investigations, concerned chiefly with the functions of the heart and brain.

It is almost a pity that the superscription, Oxford Medical Publications, occurs on the title-page. The appeal of these Lectures is to a much wider audience. Although Physiology deals with the workings of the body of man himself, it is astounding how little its teachings enter into the public consciousness. It may be that an exaggerated reticence has tended to suppress even reflection on those processes which are responsible, not only for our existence, but also for our reactions and behaviour in every phase of life. It is therefore peculiarly appropriate that the English public should have the opportunity of learning from a great Italian physiologist, who is also philosopher, artist, and man of letters, the real meaning of Physiology.

In these pages Professor Fano relates his scientific experiences almost as an autobiography. It will be seen how, from experiments made on animals such as the frog and

tortoise, lessons may be learnt, not only as to the functions of the organs of these lowly animals, but also touching the origin, life and behaviour of man himself. These Lectures illustrate also the vanity of the contrast that is often drawn between the artist and the man of science. Science has been accused of robbing the world of beauty, whereas, on the contrary, it multiplies a thousandfold the beauties which the world offers to the artist. And it is the artist in Fano that has inspired his search for order in the chaos of phenomena presented to us at first sight by living things. In his broad outlook on the data of Physiology the author is carrying out the tradition of the great physiologists and anatomists who have preceded him in Italy, among whom we can claim Leonardo da Vinci. In Physiology, as in every other science, increased knowledge means increased power, and not alone from the medical point of view, since the knowledge of how man lives will instruct us also how he ought to live. Thus, far from being merely a recondite corner of the medical curriculum, it touches closely the life of every individual, and its teachings should be a matter of concern to every type of human intellect.

The Lectures represent 'l'histoire d'un esprit,' and therefore contain individual expressions of opinion which are not necessarily of general acceptance. We seem, in fact, to make Professor Fano's personal acquaintance when we learn that he is loath to accept the conclusion, *ignoramus*, and that in such a subject as the origin of species he finds salvation, or at any rate consolation, in the assumption of a potent "cosmic will." Similar expressions, of the real import and nature of which we can form little or no definite idea, have again and again furnished convenient ledges on which the tired human spirit could rest while recovering its forces for renewed flight into and exploration of the unknown. There is no doubt that his younger readers will be fired to emulate the actual achievements of the author and to continue his adventures rather than to stay with him in his verbal retreat. Experience

and experiment have justified and continue to justify the axiom that there is no discontinuity in the chain of causation nor resting-place for those who would trace out its links.

ERNEST H. STARLING.

University College, London.

January, 1926.

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CHAPTER I

ON THE SO-CALLED "LIVING MATTER"

" . . . fra questa
Immensità s'annega il pensier mio
E il naufragar m'è dolce in questo mare." *

(" . . . my thought gets drowned in this immensity,
But it is sweet for me to shipwreck in this sea.")

CERTAIN expressions have passed into common use and have, as it were, acquired the right of citizenship in the language of science. Too often they are received with unmerited confidence because they flatter our tendency to simplify and unify. These expressions, moreover, when not hedged about with convenient reserves, act as a subtle poison of thought, cloud its critical capacities, or exalt, as anaphylactic toxins do, anomalies and deficiencies of intuition in some students. One of the commonest of these formulæ and one most used by biologists and writers on biology is that of "living matter." What may this mean? Evidently for them nothing more than the chemical composition, the physical constitution, the minute structure of a living being, or, to put it better, the sum of knowledge gained on this problem by research on living subjects.

Needless to say, our information is still superficial and incomplete, because our means of chemical, physical, and morphological investigations, in spite of constant progress, reveal at present only the most obvious facts, and these are often not the most fundamental. It could not be otherwise, given the relative coarseness of much of our actual technique. For example, if we wish to make a

* Leopardi.

chemical analysis of a living being, we are obliged to kill it before we begin. There have been, it is true, a few attempts, especially by microchemical methods, to throw light on the chemical constitution of living cells, but the results obtained in this way are, up to the present, of little importance and not very convincing. And it is obvious that analysis of an organic body immobilised by death, even if it could be complete and exact, would not enable one to identify the intermediate products of the reactions occurring during life which are probably the chemical substratum of the vital process; that is, those unstable compounds from which external and internal stimuli liberate the energy which is stored in the various structures and find expression in the different functions of the being. We are obliged, instead, to limit ourselves to the investigation of the chemical beginnings and endings of these energy-producing reactions, namely, the foodstuffs, whether for immediate use or stored, and the products of their more or less complete disintegration which are eliminated by animal or vegetable organisms or else accumulated within their frame. To the foregoing we must add researches on the materials which form bodily structure, on the synthetic processes that go to increase the reserves of dynamic material, on the products of special metabolism for defence and offence, on the catalytic tools manufactured by the organism for analysis and synthesis, and on other chemical evidences of vital activity. Some of these substances have already been isolated, analysed, and even made synthetically; those not yet obtained will probably be identified in a future not far distant. We shall then know what compounds may be extracted from the tissues after death; we shall distinguish much more clearly than now which of them serve to build up the tissues, which of them are the forerunners of dynamic manifestations and which of them result from the tissue function.

This valuable knowledge is due, and still more will be

due, to the growing contribution of chemistry to the study of organic matter. It is of the greatest advantage to biology that eminent chemists have devoted themselves to the investigation of substances extracted from organised beings, even if it be after death. The results which they have obtained in a short time are a certain guarantee of rapid progress in the near future. Their researches are directed, not only to the synthesis of special compounds, and to the knowledge of the molecular constitution of substances elaborated by chemical skill, but also to the knowledge of many intermediate products and metamorphoses which may lead to the understanding of metabolism. Progress in this direction is certain, and one day it will be possible to obtain synthetically bodies like starch and albumin.

But let us not exaggerate the biological significance of the conquests already won in this field and of the triumphs we can predict. A warning is not out of place, when we remember that the wonderful discoveries of organic synthesis and of physical chemistry, and the demonstration that the phenomena of energy in the living nearly always have their origin more or less directly in chemical reactions, have led certain eminent men of science to the conclusion that chemistry would one day build up "living matter" artificially. Chemistry, then, would provide the key to the problem, at once so tantalising and so fascinating, of the origin and ultimate nature of living beings.

To those who would allow themselves to be attracted by such a mirage, I might reply in the words of a great poet who united the highest lyrical sensibility with remarkable scientific intuition and in those of an eminent man of science, the unchallenged master of organic chemistry, whose researches, I venture to say, are as exalting as a sublime poetry.

Let me recall to you the lines which Goethe puts into the mouth of the Homunculus whom Wagner,

the pedant pupil of Faust, has just produced in his retort :

“ Das ist die Eigenschaft der Dinge :
 Natürlichem genügt das Weltall kaum,
 Was künstlich ist, verlangt geschlossnen Raum.”

(“ For this is known to be the law of matter :
 The world can scarce embrace all Nature's works,
 While those that Man hath wrought must needs be bound.”)

And Emil Fischer,¹ in summing up his admirable investigations on amino-acids, points out the small importance of certain accidental syntheses compared with the advantages which can be drawn from a well-planned research leading by slow steps towards the reproduction of a definite molecular complex. This is what he did with the so-called polypeptides. He adds :

“ Wenn es heute durch einen glücklichen Zufall mit Hülfe einer brutalen Reaktion, z.B. durch Zusammenschmelzen der Aminosäure in Gegenwart eines wasserentziehenden Mittels gelingen sollte ein echtes Protein darzustellen, und wenn es weiter möglich wäre, was noch unwahrscheinlicher ist, das künstliche Produkt mit einem natürlichen Körper zu identifizieren, so würde für die Chemie der Eiweissstoffe wenig und für die Biologie so gut wie gar nichts erreicht sein. . . .”

(“ If to-day, by a lucky chance, one should succeed with the help of a powerful reaction—*e.g.*, by dissolving together amino-acids in the presence of a dehydrating substance—in producing a genuine protein, and if it were further possible, which is still more unlikely, to identify the artificial product with a natural substance, but little would be attained as regards the chemistry of proteins, and less than nothing as regards biology. . . .”)

And let it not be forgotten that these proteins, apparently so stable, show a remarkable plasticity. Consequently they assume a variety of aspects and endow the organism with manifold powers of resistance. To show that, it is enough to mention the processes which develop

under various influences in the blood-plasma, determining the formation of antibodies, agglutinins, precipitins, opsonins, and many other products. The organism is thus rendered resistant to the action of chemical and morphological agencies which otherwise would destroy it.

In this connection, I may be permitted to recall that it was during my researches on blood-plasma that the formation of an antibody was first demonstrated. I would not allow myself to make this statement were it not that it has been published, though obviously in a too flattering manner, by Camus and Gley ² in a work on anticoagulants. They say :

“Dès le début presque de nos recherches sur l'action des solutions d'albumose sur la coagulabilité du sang, nous avons soutenu qu'à la suite d'une injection de ces substances il se forme dans l'organisme un corps qui se comporte comme un antagoniste de la plasmase. L'incoagulabilité du sang consécutive à une injection d'une peptone de commerce, telle que la peptone de Witte, s'expliquerait donc par la production d'un anticorps s'opposant à l'action du ferment coagulant du sang.

“A cet égard Giulio Fano a été un précurseur. En montrant que le sang des animaux peptonisés (chiens), traité par l'eau ou par l'anhydride carbonique, se coagule et par conséquent qu'il contient tous les éléments nécessaires à la formation du caillot, et d'autre part et plus encore, en montrant que le plasma sanguin ou la lymphe du chien peptonisé empêche *in vitro* la coagulation du sang du lapin, animal réfractaire, comme on le sait, à l'action de la peptone, G. Fano établissait deux faits très importants pour l'ensemble de nos connaissances sur le mode d'action des substances anticoagulantes. Et en même temps, comme Gley eut l'occasion de l'affirmer dans la discussion qu'il soutint en 1896 à la Société de Biologie sur cette dernière question, il fournissait le premier exemple d'un antigène et d'un anticorps.”

(“Almost from the commencement of our researches on the action of solutions of albumoses on the coagulability of the blood we have maintained that, following an injection of these substances, there is formed in the organism

a body which behaves as an antagonist of thrombin. The non-coagulation of blood following an injection of commercial peptone, such as Witte's peptone, would therefore be explained by the production of an antibody which would oppose the action of the coagulating ferment in the blood.

"In this subject, Giulio Fano has been a pioneer. By showing that the blood of peptonised animals (dogs), when treated with water or carbonic anhydride, coagulates, and consequently that it contains all the elements necessary for the formation of clot, and, further, which is still more important, by showing that the blood-plasma or the lymph of a peptonised dog prevents *in vitro* the coagulation of rabbit's blood, an animal which, as is known, is refractory to the action of peptone, he established two facts of great importance to the sum of our knowledge of the mode of action of anti-coagulants. At the same time, as Gley had occasion to state in the discussion which he led in 1896 at the Société de Biologie on this question, Fano gave the first example of an antigen and an antibody.")

The texture of a living being must be considered, not only from the chemical, but also from the physical and physico-chemical points of view. Living beings, in order to maintain or defend their individual and racial integrity, must be capable of reacting promptly and effectively, consciously or unconsciously, to the favourable or unfavourable accidents of their environment. To this end, they are endowed with a considerable energetic potential, with great instability, and, in relation to their mass, with a large surface. The latter enables them readily to make use of the first two attributes. This tendency to the development of a large superficies is observed, not only in the division into cells of the protoplasmic and nuclear material of which we shall speak later, but also in the peculiar state of aggregation of the substances forming their chemical and physical substratum. Apart from the supporting or protecting tissues, we may consider the living cells and the fluids impregnating and surrounding them as consisting of colloids which in the tissues are divided into

compartments by means of membranes of variable permeability for electrolytes or for other substances.

The colloidal state is a condition in which ultramicroscopic particles—the tagmata or micellæ—are suspended in a liquid with which they are immiscible; they are animated by Brownian movement. Thus there are two phases in intimate contact: the outer, or continuous, formed by the surrounding intermicellar liquid, and the internal, or dispersed, represented by the suspended matter. We are concerned, in other words, with a heterogeneous system having vastly extended surfaces of contact, not easily separated by mechanical means, between the two phases. It is evident that the chief characteristics of the colloidal state are derived from the enormous extent of the surfaces, corresponding, in an adult man, to an area of many millions of square feet, through which are effected the exchanges necessary to life. One can understand, therefore, that the colloidal state shows considerable instability. It is the seat of processes dependent on changes of surface tension, such as the electric potential, imbibition and superficial condensation, special behaviour of the electrolytes, and so on. It may therefore be said that the colloidal state represents a dynamic state of matter, whereas crystalloid is a static condition. Obviously then, in investigating the phenomena of life, attention must be centred on the properties of the emulsoid state peculiar to tissues and humours. The particles in these colloids contain an insoluble nucleus surrounded by soluble substances which are attached to it by surface condensation. Thanks to the great dispersion of these particles, the colloids present, as has been said, so large a surface as to allow of the speed and intensity of certain vital reactions. Besides, it is evident that the complexity of the suspended particles, which are gigantic when compared to the molecules of a crystalloid, and their innumerable chemical possibilities, give the best possible conditions for bringing about a great variety of reactions. They determine a peculiar surrounding

medium also, in which chemical reactions develop in a different way from ordinary solutions. One could give many examples of this, some of which were the result of researches pursued by Prof. Paolo Enriques and myself on the so-called saline-protein compounds.³

Another point must be kept in mind in connection with the colloidal state. Chemical reactions during life take place at a temperature which is usually less than 40° C. and in indifferent media, whereas they cannot be repeated *in vitro* except at high temperatures and with very active reagents. From numerous researches it seems probable that the above-mentioned advantage is to be attributed to the capacity of living beings to produce and make use of enzymes. These accelerate the reactions to the point practically of determining them; at the same time they do not themselves take part in the final equilibrium.

Enzymes bring about a great variety of reactions and are extremely widespread. They act on divers substances, splitting them up and causing hydration or hydrolysis, coagulation or liquefaction, oxidation or reduction, or even activating other enzymes which, of themselves, would remain inert. They appear in the digestive tract, determining those hydrolytic actions on the food-stuffs which represents the first phase of metabolism. We therefore surmise that the oxidation of the final phase is also due to their power of rendering oxygen active.

Nor must it be forgotten that, owing to the reversible reaction which takes place in fermentative processes, not only the splitting up of compounds, but also their synthesis may be attributed, in part at least, to similar catalytic agents.

Among the numerous theories put forward to explain the action of enzymes, perhaps the most probable is that which attributes the phenomenon to a molecular concentration determined by the dispersed phase in certain colloids. Through them the substances participating in the reaction would invade each other's sphere of action,

as happens when a finely-divided metal such as spongy platinum is used. This representation of fermentative processes as the result of superficial concentrations may seem artificial, especially when their specificity, albeit relative and still under discussion, is taken into account. Yet it seems indubitable that the properties belonging to the surface, *i.e.*, the nature of the substances which form it, their position and residual affinities, and the resulting combinations and condensations, must be considered among the determining factors of enzyme action.

This investigation of enzymes is without doubt one of the most fundamental in physiology. From their study we may expect, not only knowledge of the course of many chemical reactions, analytic and synthetic, but also perhaps of certain histogenetic processes, at any rate of the simpler ones, *e.g.*, the formation of scar tissue. The beginning of the latter, in fact, often consists of coagulation of extravasated blood due to the action of specific enzymes, and even in the later stages we cannot deny that the influence of white corpuscles and finally of the platelets may be essentially due to ferments. There is always present to my mind an impression received during the early days of my researches in physiology when I observed under the microscope that peptonised plasma, incoagulable when left to itself, is made to coagulate by diluting it with distilled water. In this experiment one finds that from the leucocytes and platelets present in the liquid fibrinous filaments radiate which soon form a reticulum like that of adenoid tissue. The mind receives the impression of looking on at the building of a tissue, albeit a rudimentary one. At any rate, it represents the formation of a sort of intercellular substance derived from specific protein bodies under the probable influence of enzymes extracted from the leucocytes and platelets by the distilled water. And since I have thought fit to suggest the possibility of the intervention of enzymes in histogenetic processes, I may be permitted, in support of my suggestion, to recall the

obvious influence, quantitative and qualitative, of certain hormones, especially of the thyroid, the pituitary, and the interstitial bodies in determining the characters and relations of morphological manifestations.

Although I would not assert that any of the hormones is a catalytic agent, yet they afford an example of oligodynamic action; since, when they penetrate into the blood-stream, even in minimal quantities, they may produce powerful effects on the general metabolism. Thus, besides their effect on energy and mental capacity, they influence the morphological relations and functions which contribute to the form and dimension of the body as a whole and of its various parts.

Our knowledge of the colloidal state, especially regarding the development of its surfaces and its consequent instability, may also enable us to form some idea of other processes, for example, the nature of colloidoclastic shock in anaphylactic conditions.

Schmidt-Mülheim and I were the first to study this extraordinary reaction. While investigating the phenomena following an injection of peptone sufficient to prevent coagulation of blood in the dog, we noted the simultaneous occurrence of a considerable fall in the blood pressure, a state of profound narcosis and marked intestinal congestion with severe diarrhoea. Later I continued on my own account these studies and demonstrated the presence in peptonised plasma of an anticoagulant which was, as has been said above, the first example of an antibody.⁴

But at that time the facts of anaphylaxis were not known. They were brought to light by the genius and initiative of Richet, who drew the attention of many workers to the subject. From recent investigations, it would seem that anaphylactic shock is to be attributed to the penetration into the circulation of a heterogeneous substance or probably to a physical action causing dislocation or disequilibrium or in some other way upsetting the normal relations between the molecular aggregates of the body humours.

It will be recollected that cold also may determine similar effects, as happens in paroxysmal hæmoglobinuria or in the common coryza. It would seem that the suspended particles, either by their electric potential, or by some other quality which escapes our investigations, have definite relations among themselves. These qualities confer upon the fluids of the organism a special constitution which may vary in different individuals. In this way we may represent to ourselves the conditions determining the idiosyncrasies and the special anaphylactic sensitiveness of single individuals which were attributed to a special tendency of certain colloids towards flocculation. These speculations have a great fascination; they lead to research and, as a consequence, to new therapeutic measures. The phenomena of anaphylaxis are, however, in great part unexplained. They make us realise our ignorance, not only of the chemistry and the physical properties of the fluids in the body, but also of the influence exercised by the physico-chemical state on all the manifestations of life.

The mystery which wraps us round deepens more and more when we consider the exchanges of matter taking place continuously between the cells and the surrounding fluids. The latter have passed through the superficial layers of protoplasm, which are differentiated in places to form well-defined morphological membranes. The conditions are always highly mutable, because the cell membrane may have a selective action owing to its special mechanical, physical, chemical, or structural properties. The factors to be taken into account are the electric potential, the size and dimension of the pores, the special solvent properties, the various affinities of the complicated chemical substances of which the membrane is composed, and other conditions besides. Any or all of these may alter the permeability of a cellular membrane; they may allow certain substances to pass rather than others, let them pass as they are, or modify

them in passage. When one thinks of the numerous secondary valencies of a protein molecule and of the innumerable bonds that it may in consequence contract with different organic and inorganic substances, it is easy to imagine how many relations may exist between the components of the membrane, the substances present in the fluid outside the cell and those which form its contents. So that it may come about that certain substances found only in minute quantities in the surrounding fluids are taken up largely and that others, which, on the other hand, may be abundantly represented there, are not found among the chemical compounds of the protoplasm and nucleus within; or it may be that compounds which reach the cell are different from those in the surrounding fluid, because they have been modified during their passage through the membrane. Thus the cell membrane, which is the result of external and internal conditions, appears as a very variable partition changing with every alteration in its surroundings. It adapts itself to the immediate needs of the cell which it bounds, becoming, according to the exigencies of the moment, permeable or impermeable to crystalloids and to some more than others, and ultimately and above all to colloids. So, if cell membranes seem to us to be always semi-permeable, it only shows that our experiments are made under conditions rendered artificially stable, and not comparable to those ordinarily present *in vivo*. All membranes, thanks to their mutability, adapt themselves to varied circumstances, affording a striking instance of the teleological law of Pflüger as to the result of the behaviour of living beings: "The cause of every need of a living organism is at the same time the cause of the satisfaction of this need." ⁵

I have prolonged this argument at some length in order to show the advantages, from some points of view, of applying chemico-physical research to living beings. I will not deny, however, that these have perhaps contributed to develop the love of cut-and-dried schemes in biology, giving

the prestige of a scientific appearance to a simplification which subordinates the interpretation of physiological facts to an unseasonable desire for a definitive explanation. This tendency is as dangerous as it is attractive. Exponents of this school might, for instance, consider protoplasm merely as gelatine and not give sufficient weight to its complex physical, chemical, and structural constitution, its instability, the plasticity of its phases, its atavism, its reproductive capacity, its ceaseless evolution; they would attribute to cell membranes permanent properties which in reality are often merely the expression of a momentary phase, fixed at times by experimental artefact.

But the difficulties of investigating the constitution of organic matter do not end here. It is not only the variety and complexity of the chemical compounds in the body, their innumerable and divers relations, the instability of intermediate products, the colloidal state of the protoplasm and surrounding fluid, the multiform catalytic actions, the variability of membranes that make up the difficulties of the chemical problems of living beings. Living beings are not limited to the accumulation of dynamic material and the liberation from it of the energy necessary to their functions; they do not merely form intermediate chemical instruments for vigorous catalytic action. One of their most characteristic activities is to build a structural mechanism, which takes up and transforms certain external energies, liberating them by means of disintegrative processes, determining moreover the conditions necessary to open the way for and to associate the various functions.

These histogenetic powers complicate greatly the problem, already so intricate, of the chemistry of living beings. For the chemical analysis of an organised body, it is necessary not only to employ reagents of great destructive force, which give a deformed image of the chemical composition of the living being; one is also obliged to destroy the chemical basis of the structure. Let us consider, for instance, the two most fully studied examples of

catalytic agents, derived respectively from the animal and vegetable kingdom—viz. hæmoglobin and chlorophyll—chemically allied and functionally antagonistic; the one is an oxidising, the other a reducing agent, owing perhaps to the presence in them of iron and magnesium respectively. But hæmoglobin, at any rate in vertebrates, is an integral part of the red cells, cells differentiated so as to increase their superficial area and therefore facilitate its function of intermediary between the oxygen of the air and the tissues; the same morphological element, with its hæmoglobin, contributes besides to other more complex exchanges, at whose nature we can for the most part hardly guess. By means of special solvents it is possible to extract hæmoglobin from the erythrocyte, which is then reduced to a protoplasmic envelope—the stroma. But this is not a sufficient reason for stating that red cells consist of hæmoglobin and stroma contained one in the other, for, in reality, hæmoglobin and stroma have no separate existence, but are one living element united chemically, morphologically, and functionally. We will not enter into the history of the metamorphoses undergone by the red cell, before reaching its definitive state. Even when development is complete, it passes through many changes, and it offers a numerous and complicated series of problems, not only as an isolated morphological entity, but also in its relations to the organism as a whole and especially to the hæmatopoietic organs.

Analogous observations might be made with regard to chlorophyll. Need I try to record the vast diversity of forms of chloroplasts and of chlorophyll cells, the infinite variety of leaves formed according to the special necessity of assimilation of the various plants, and of the different atmospheric conditions in which they live? And, further, need I mention the part taken by chlorophyll in the process of assimilation, not only as a specific filter of the sun's rays, but also as an integral part of the chloroplasts?

And it is to be observed that in the examples I have quoted, we had to do with cells which are in relation with the rest of the organism only through tissue fluids. These relations, though presumably not as complicated as are those of nervous tissue, are yet far from being completely understood. La Rochefoucauld, at the end of the seventeenth century, expressed a truth in his maxim :

"Les humeurs du corps ont un cours ordinaire et réglé qui meut et tourne imperceptiblement un empire secret en nous, de sorte qu'elles ont une part considérable à toutes nos actions sans que nous la puissions connaître."

("The humours of the body have an ordinary regular course, which imperceptibly moves and sways a secret force within us, so that they have a considerable share in all our actions without our being aware of it.")

How enthusiastically would he have upheld the influence of organic fluids had he known of the results of research on humoral correlations gathered in the last thirty years! We who have watched their development are filled at once with humility and pride.

Let us take, for example, the physiological action of a relatively simple substance—adrenin, which may be considered as a methylamine derivative of pyrocatechol. It contains an asymmetrical carbon atom and therefore presents two optical isomers. Of these, the *lævorotatory* was extracted from the chromaffin cells contained in the medulla of the suprarenal gland. The racemic product obtained by synthesis is much less active, since the *dextrorotatory* form is twelve times less potent than the *lævorotatory*. I will not enter into the question of the morphological and functional analogies of the chromaffin body with the sympathetic system. Although there are some who, basing their arguments on experimental evidence, have questioned the neuro-secretory theory of the chromaffin tissue, there is no doubt that one injection of the minimal dose of adrenin, a 400th of a

milligram per kilo body-weight, gives results which explain the complex mechanisms of adaptation. The abdominal vessels contract and at the same time the coronaries relax, thereby reinforcing the action of the heart-muscle; simultaneously, in the liver, larger quantities of glycogen are transformed into sugar. It is easy to understand the reason for this association of activities; when special conditions lead us to react with increased muscular action, a stimulus from the sympathetic arouses the function of the chromaffin body and a certain quantity of adrenin is poured into the blood. The result is a quickening of circulation, a constriction of the splanchnic vessels, and therefore a greater flow of blood to the muscles. At the same time, owing to the more rapid transformation of hepatic glycogen, more glucose is placed at their disposal. How can we with our limited knowledge represent chemically such a marvellous series of adaptations? Owing to the presence in the blood of an infinitesimal quantity of a specific hormone, the skeletal muscles are placed in the best conditions to respond readily to the demands of the will; they receive a larger quantity of blood, containing a greater amount of glucose. This is really a reaction specific to adrenin. If instead a salt of barium is introduced into the circulation, the result is a general contraction of all smooth muscles which has no functional correlation.

The sympathico-mimetic action of adrenin would seem to be mainly dependent on the presence of an amino-group which is united to the benzene ring by the intervention of another group. It is somewhat analogous to that of certain poisons and the antagonisms relating to poisons of the terminal connections of the cranial and sacral autonomic systems on the one hand, and on the sympathetic on the other. We know, indeed, that the neuro-muscular functions of the cranial and sacral nerves are stimulated by pilocarpine and paralysed by atropine; the sympathetic system is not affected by these poisons, but is stimulated by adrenin and paralysed by

choline. Thus atropine dilates the pupil by paralysing the endings of the ciliary nerves and pilocarpine contracts it by stimulating them, whereas the mydriasis obtained with adrenin is due to stimulation of the terminations of the sympathetic. This antagonistic action of poisons usually runs parallel to a corresponding antagonism of function, since organs endowed with double innervation—autonomic and sympathetic—generally receive their excitomotor nerves from one system and inhibitory nerves from

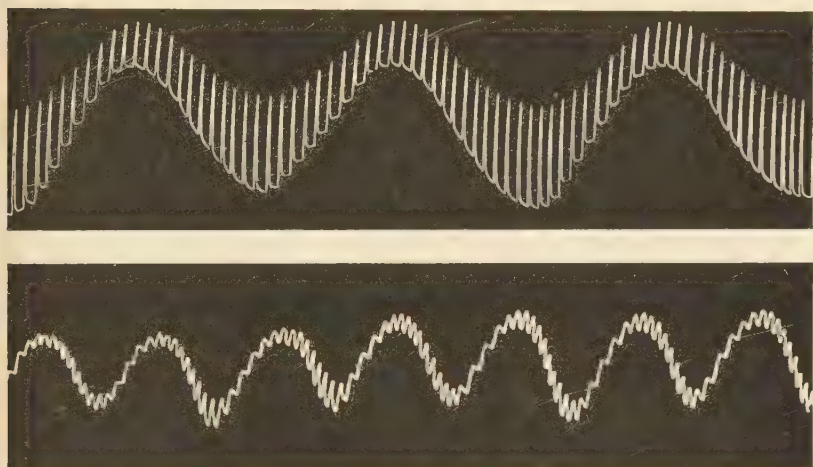


FIG. 1.—Tracing obtained by means of a registering lever attached to the apex of the pulsating auricle of *Emys europaea*. The more rapid oscillations correspond to the ordinary rhythm, the slower to the oscillations in tonus.

the other. This is observed, for example, in the innervation of the iris, of the blood-vessels of the head, of the salivary glands, and of the heart. It is proved, as regards the heart, by the relations between the rhythmic function of the auricles of *Emys europaea* and the much slower contractions which I first observed in these organs, and which I have called oscillations of auricular tonus⁶ (see Fig. 1). In the auricle, the stimulation of the vagus inhibits the fundamental rhythm and intensifies the

oscillation of the tonus; the opposite occurs on stimulating the cardiac sympathetic. The same antagonism is observed in testing different poisons, according to whether they excite or paralyse the functioning innervated by the autonomic cranio-bulbar system—the vagus, or the thoraco-lumbar system—the sympathetic. Analogous effects may be obtained with physical agents. Heat accelerates the fundamental rhythm and decreases the oscillations of the tonus, and the contrary happens when cold is applied. If the effect of adrenin is tried on the double contractile function of the auricles of the heart in marsh tortoises, it is easy to observe that it stimulates the sympathetic nerve-endings, as is shown by acceleration of the fundamental rhythm, and inhibits the terminal apparatus of the vagus, shown by a decrease in oscillations of the tonus. It is therefore evident that in this case adrenin produces the same effects produced by stimulation of the sympathetic and by inhibition of the antagonistic nerve-supply represented by the endings of the vagus. Without wishing to generalise too far, one may conclude from these facts that, at any rate in some cases, organs endowed with double innervation, autonomous and sympathetic, are able to react to substances introduced from outside or elaborated by the organism, and that the effects are intensified because, besides liberating the determinants of one function, the chemical stimuli inhibit the action of their antagonists, thus ensuring ready and complete carrying out of any functional act.

What has been said of the action of drugs, and especially of adrenin, becomes even more suggestive if we compare it with the effects resulting from poisoning of the neuromuscular apparatus by nicotine and curare. Indeed, from the study of the peculiar selective action of these poisons, has emerged a hypothesis on the mechanism of the transmission of impulses from the nerve-endings to the organ which they supply.

This doctrine can be associated with the much-discussed

and debatable theory of side chains, which represents certain physiological manifestations by means of symbols analogous to those used in organic chemistry. Everyone knows how chemical researches have led us to the belief that the special properties of a compound are due to radicals or groups of atoms joined secondarily to a more or less complex central nucleus; and how, in order to alter the chemical properties of such a compound, one can change or substitute one or more of these secondary groups.

In applying to biology, with considerable reservation, this hypothesis which has been so fruitful in chemistry, it has been assumed that protoplasm consists of a central nucleus in which reside the fundamental functions of exchange, and therefore of the production of energy of the structural elements. Specific characteristics, on the other hand, are determined by groups, or side chains, or receptors, capable of combining with foreign substances stimulating in different ways, such as poisons, medicaments, food-stuffs, and so on. In this way, a particular function might be aroused, inhibited, paralysed, excited or otherwise modified, without injuring the vital continuity of the central nucleus. If the latter were broken up, the protoplasm would perish, just as in complex organic compounds the breaking up of the central nucleus leads to combinations fundamentally different from those of the original substance. It is principally to an English physiologist, Langley, that we owe the researches which led to the theory, proposed by himself, of receptor substances. He showed that nicotine provokes a prolonged contraction of certain muscles even after the degeneration of their innervating fibres, and that this state of contraction could be diminished if curare was afterwards applied. Since this antagonistic action is observed when the nerve-endings in the muscle are degenerated, and when, in spite of the action of the poisons, the muscle continues to contract if directly stimulated, Langley concluded that the above-mentioned drugs did

not act directly on the contractile material, but on a substance designed to transmit the impulse from the nerve to the muscle—*i.e.*, the receptor substance.

The receptor substance is said to be connected with the so-called synaptic membrane situated between the end plate and the muscle fibre, which is supposed to arrest the degenerative process. So that in all cells, to put it in Langley's words :

“ Two constituent parts at least must be distinguished, (1) substances concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products, and (2) receptive substances especially liable to change and capable of setting the chief substance in action. Further, that nicotine, curare, atropine, pilocarpine, strychnine, and most other alkaloids, as well as the effective material of internal secretions produce their effects by combining with the receptive substances, and not by an action on axon-endings if these are present, nor by a direct action on the chief substance.”

In conformity to the above-mentioned facts, it is now possible for us to gain some idea, for example, of the transmission of the state of excitation from nerve to muscle causing contraction. This would result by a process similar to that of internal secretion, *i.e.*, it would be determined by the nervous stimulus on the connecting apparatus between nerve- and muscle-fibres. The substance thus formed and liberated, combining with the special receptor radicals of the contractile material, would detach them, causing the muscle-fibre to pass from a state of relaxation to one of contraction. The fibre, assuming adequate nourishment from the tissue fluids, would reconstruct the lost radicals and thus reacquire the capacity for further mechanical action.

The specific effects of nicotine and curare on the pre-ganglionic synapses of the autonomous system and on the terminal organs of motor nerves seem to give special support

to these conceptions. By them we could explain to ourselves the selective action of these poisons, as the result of their combination with the different side chains which we imagine to be the chemical foundation of the specific properties of particular tissues. Adrenin would act in the same way as a substitute of the product usually secreted in consequence of nervous stimulation of the neuro-muscular endings; it replaces it by combining with special receptors and provoking muscular contraction.

The chromaffin bodies then could give us an example on a large scale of the transmission of a stimulus from nerve to muscle by the specific action of a hormone on particular receptors. In this case, the contraction is due to a nervous stimulus which does not act directly on the contractile structures, but excites the secretion of a substance which, carried by the blood, comes in contact with special receptors. By combining with them, it determines the same effects which would follow direct stimulation of the ramifications of the sympathetic innervating these tissues. The chromaffin bodies, in their relations with special contractile elements, should therefore be considered analogous to an enormous conjunction apparatus between the sympathetic system and the innumerable elements of smooth muscle. The only evident difference which distinguishes them from ordinary receptor organs is that they act at a distance, making use of the blood-stream as a means of transport.

From what we have said, there is shown a certain analogy of mechanism between the nervous and humoral transmission of impulses. Accepting the mechanism of action of the chromaffin bodies, just described, we have an argument in favour of the theory which represents nervous stimulation of muscle as the result of a combination between the substances secreted by the neuro-muscular apparatus and the special receptors of the contractile material.

But conductions by way of humours occur under different circumstances from conductions by means of nervous

stimuli. When localised, rapid and delicately graduated effects are required, as in voluntary or automatic action and in numerous reflex actions, the nervous mechanism is exclusively used. It meets the requirements of these functions in being rapidly conducted, isolated, subtly regulated and consists of impulses from the centre to the periphery and *vice versa*, or between central elements among themselves. In other circumstances, when this is not necessary, the nervous system assumes as intermediary special internal secretory organs and pours into the blood a specific hormone, *e.g.*, adrenin, which causes a diffuse constriction of blood-vessels.

But these products of internal secretion, these hormones elaborated by various endocrine glands, *i.e.*, the supra-renals, thyroid, thymus, the interstitial portion of the sex glands, the hypophysis, and others as well, are not limited in their actions and correlations to those we have mentioned in speaking of adrenin. As is known, the internal secretions not only influence the motor, secretory, and nervous activity, but also directly or indirectly, direct and co-ordinate the constructive forces which during development form, and during adult life maintain, the individual in conformity with a model which may be considered the somatic and functional ideal of the species. Therefore a lesion or an alteration of equilibrium in the endocrine constitution may give rise, especially during development, to anomalies of structure and function, so that instead of a normal being we have a dwarf, a giant, or a cretin. It is possible, in part at least, to avoid these serious consequences, by injecting extracts of endocrine organs. The results obtained up to now by experimental or therapeutic methods give good ground for hope of a remarkable future for opotherapy, to the advantage and increase of energetic, psychic, or morphogenetic capacities.⁷

Before concluding this rapid survey of the field of humoral reactions, I would bring to your notice how certain morphological elements normally complete their

cycle of life though separated from any direct nervous control but receiving only through the influence of the surrounding medium, the remote echo of the general life of the organism to which they belong. I refer to the leucocytes, which, even in the adult, preserve the character of embryonic cells, and the erythrocytes almost crystallised in their relative simplicity of function. Experiments on excised tissues show that other elements when isolated behave differently. If they are cultivated in specific gelatine plasma frequently renewed, tissues may survive many months and eventually grow and reproduce themselves.⁸ Investigations show that differentiated elements which are united to the rest of the organism by normal circulatory and nervous bonds maintain their individual structure and do not reproduce themselves, or only within well-defined limits. On the other hand, surviving isolated tissues may show an unlimited tendency to reproduction. When this happens, the successive generations gradually may lose their specific morphological characters, becoming de-differentiated, as one may say, *i.e.*, assuming the appearance of undifferentiated embryonic cells. Just as the tissues are built up through stages of increasing differentiation, so, when the reverse takes place, the tissues gradually revert to the embryonic type. But something remains of the original constitution of these surviving and growing elements. They lose their morphological outline, but they maintain the specific chemical characters of the animal to which they belonged; for they die when cultivated in heterogeneous plasma, *i.e.*, plasma obtained from an animal of a different species. Occasionally the plasma of a nearly allied species may suffice, but survival is then of short duration.

This tendency of isolated cells to reproduce themselves in unlimited fashion, even when they belong to tissues which in the organism would not show any reproductive capacity and degenerating as they grow, reminds one of what is seen in malignant tumours. Tumours, moreover,

are caused by an excessive proliferation of cells which become at the same time more or less atypical. It is enough to mention the most terrible scourge which afflicts humanity to realise the great importance, practical as well as theoretical, of these investigations. From them we have learnt that the cells of tissues and the organs which they make up, when they are isolated and kept under conditions which ensure survival, behave as if they were no longer subject to the action of special directive actions which, diffuse or centralised, continuous or temporary, according to the grade of development of the being, determine and fix its form, size, and minute structure. These directive actions, obviously of nervous origin, not only maintain the special character and form of the tissues and organs, but may also intervene in some cases to bring about repair, and reveal a capacity for adaptation to exceptional conditions. Take, for example, the heteromorphic regeneration of the crystalline lens of the triton, which after extirpation grows again by a process quite different from that followed in its normal embryonic development. In the whole series of vertebrates, the tissue from which it is reconstructed has never, under normal conditions, participated in the formation of a lens.⁹

But the new formation of an organ demanding special dioptric properties, obtained by means having no connection with its embryonic predecessor and occurring only in inferior vertebrates, is obviously the product of very complex freeing actions which at present we are completely unable to understand. In higher animals, on the other hand, in normal conditions, or in order to adapt themselves to accidental circumstances, we observe formations of new tissue which are termed hypertrophy, if the enlargement of the organ is due to the increase of the dimensions of its cells, or hyperplasia, if it is due to their multiplication. When obstacles to the circulation arise, the heart hypertrophies in response to the

heavier mechanical work required; after removal of one kidney, the other kidney enlarges to cope adequately with the increased excretion demanded of it. Other examples could be given, but we will limit ourselves to the closer examination of a very common instance which is within the sphere of physiology, that of the voluntary muscles. The contractile tissues that are under the domination of the will carry out movements which are the most tangible manifestations of daily activity. Everyday experience teaches us that with prolonged rest they undergo a diminution of their volume, *i.e.*, atrophy, while repeated activity causes an increase in size—hypertrophy. Compare, for example, the biceps of a clerk with that of a wrestler or an acrobat. What stimuli determine the neoformative or trophic processes manifested in muscular hypertrophy? Evidently these stimuli are derived from muscular activity and may arise from physical or chemical processes which precede, accompany, or follow the contraction, and which directly, or by way of tissue humours or nerves, stimulate the building up of tissue. The proposition might carry us far; following Hering and, in conformity with my own observations,¹⁰ I tentatively suggest that they are chemical stimuli, *viz.*, katabolites, products derived from processes of disintegration, which liberate the energy used by the muscle in contraction. Let us not forget that the muscles are the seat of continuous disintegrative actions, even when apparently at rest, because by a continuous katabolic process they provide the chief contribution to the production of heat which in higher vertebrates keeps the internal temperature constant. If it is admitted that katabolites liberated during apparent rest are insufficient to maintain the trophic equilibrium of the muscles, it will be understood how they atrophy from excessive rest, maintain a particular equilibrium with ordinary activity, and how more intense work causes hypertrophy. It is therefore on the quota of functional activity of an organ that its structural

equilibrium depends, and we find here an example of that reciprocity between structure and function which is a fundamental principle of the phenomena of life.

Hence it is evident that the innumerable structural elements variously grouped to form the tissues and organs, the apparatus and systems of the body, are not independent units, but are closely dependent on circulatory and nervous influences, whence result not only their functional capacities, but also their specific structure. Besides these extrinsic relations, many of the connective-tissue elements as well as epithelium, nerve, and muscle resemble cells of the vegetable kingdom in being united to each other by special prolongations or ramifications bridging the gaps from cell to cell. Therefore many tissues are the result, not of an association of separate and distinct units, but rather of a protoplasmic reticulum specifically differentiated, in which, at nodal points, the cells enclose a certain amount of nuclear material. For this reason, cellular division which is present from the beginnings of embryonic life does not always determine the formation of separate and distinct elements, but continuous connections are often left in spite of division and growth.

Thus we have a minute subdivision of protoplasmic and nuclear material which answers morphologically to the functional needs of the being, providing an enormous increase of surface in comparison with its mass.

Living beings, and I wish to emphasise this point, are constantly traversed by currents of energy which constitute the dynamic substratum of their function; it is necessary therefore that they should readily assimilate food-stuffs and the oxygen wherewith to oxidise them, and excrete the products of their activity. It must besides be easily reached by stimuli releasing its functions and must react promptly according to the needs of the moment. Finally, it must, as far as possible, maintain immediate reciprocal relations between protoplasm and nucleus, so that

the protoplasm may be influenced by the hereditary characters of the nucleus and that the process of disintegration that releases energy may be promptly and vigorously repaired. The division of the organism into minute protoplasmic corpuscles enclosing one or more nuclear nodules enables it to respond effectively to these functional demands, while the incompleteness of the subdivisions corresponds to the other functional necessity of association and motion.

For these reasons we are not justified in supposing that the properties of isolated tissues correspond exactly to those shown by the same elements when they form an integral part of the organism and are influenced in divers ways. Still less should we follow those who consider the cell as a structural unit maintaining an independent existence. This would be the same as to say that individuals of the human society can live in isolation after the romantic manner of Robinson Crusoe.

And still less is it possible to compare single structural elements with protista, for the specious reason that they are made up of a single cell. These organisms are monocellular because their small size allows of sufficient development of surface in relation to their mass. But in their one cell they may present complicated differentiations of organs and apparatus.

Therefore, to liken a protist to a body-cell seems to me unsound, and all the more so when the study of the properties of cells and protista taken together are made the subject of general physiology. On the contrary, for technical and theoretical reasons the general physiologist should give most attention to animals of higher and more complex structure on which it is much less difficult to experiment, whose functions are more clearly differentiated and can better reveal their cause and significance. In these researches we must also attempt to establish analogies between conscious and unconscious acts, daring to examine psychic phenomena, not only from the point of view

of determinism, but also as a conscious state such as is revealed to us by introspection. This may illumine in a very suggestive manner the motives of vital acts.

To investigate the relationship between the multiform manifestations of fundamental functions of all living beings, plants and animals, protozoa and metazoa, to remove from them the individual mask which conceals their general characters, to establish their common physical, chemical, and possibly morphological and teleological basis—this would seem to be the tremendous task of general physiology, and not that of investigating exclusively the functions of living beings and of structures conventionally defined and associated.

CHAPTER II

AGAIN ON THE SO-CALLED "LIVING MATTER"

FROM the foregoing it is evident that one could continue indefinitely to give examples of biological phenomena which are obviously functional adaptations, although we do not know how the greater part of them are brought about. While avoiding the important controversial question of the psyche, may it not be hoped that through the study of the chemical, physical, and morphological processes of living beings we may gain knowledge of the factors that set in motion and co-ordinate the processes of life? Should we consider living beings merely as a jumble of chemical substances which, like crystals, are polarised in structural forms by factors deriving from conditions intrinsic to the substances or due to their reciprocal relations? Or should we see in the various structures only the effects of unequal surface tensions, or of greater or less imbibition of gelatine, or of a grouping of similar molecules? And, if this were so—which we may doubt—can we believe to-day in the prospective power of chemistry to solve such momentous problems? Chemistry is still in great measure an empirical science. It is almost as intuitive as biology. When confronted with complicated problems it finds itself as Van't Hoff says: "*bei den geheimnissvollen Verhältnissen wo nur der wundervolle instinkt des Chemikers den Weg zu finden weiss*" ("among those mysterious relations where only the wonderful instinct of the chemist can find a path").¹¹

But the phenomena of life are much more complex than the foregoing remarks suggest; because the chemical

operations by which potential energy is stored or accumulated energy is released, and those which provide the material substratum of the structural buildings, appear in the mass to have an indisputable teleological significance. In their ensemble they reveal what is really the living being, a highly complicated mechanism, following a definite cycle of growth, of equilibrium, and of involution, and which, during the whole course of its existence, battles ceaselessly against innumerable and different antagonists, external and internal, to defend its integrity, first as an individual and, secondly, as a member of society, for the preservation of the species to which it belongs. The ceaseless struggle is fought more often unconsciously, in the obscurity of the tissues, than by the light of the will. As soon as the marvellous co-ordination of effort ceases, the organism dies and becomes a prey to myriads of germs, the saprophytes, which rapidly dissolve it into a foul and repulsive carrion. Therefore it is the teleological character evident in every energetic or histogenic action of the organism which reveals its specific nature. This characteristic finality of its behaviour cannot be put in any logical relation with the chemical and physico-chemical properties of material extracted from its tissues. This is even more obvious, if one considers in a given organism, not merely its own individuality, but also what it represents and signifies in the animal scale. Claude Bernard, one of the greatest physiologists of last century, was inspired to say :

“ Dans tout germe vivant il y a une idée créatrice qui se développe et se manifeste par l'organisation. Pendant toute sa durée, l'être vivant reste sous l'influence de cette même force créatrice, et la mort arrive lorsqu'elle ne peut plus se réaliser.” ¹²

(“ In every living germ there is a creative idea which is developed and revealed by organisation. While it lasts the living being remains under the influence of this same vital creative force, and death supervenes when it can no longer be realised.”)

And in consequence what may we consider as living matter? Where may we seek it? It is obvious that we must conceive it as that which, with suitable selection and elaboration, takes up nutritive material and uses it, which forges its catalytic and structural instruments, which reproduces itself, jealously guarding its hereditary characters, yet adapting itself with ease to the needs of the moment, which determines psychic phenomena and thence the individual's ideas of the external and internal world. In its highest manifestation it rises to the intellectual capacity of man, co-ordinating individual forces towards collective and progressive action. This transformer of energy and architect of form always directed towards definite ends, in unceasing evolution, so evidently moved through dynamic and structural means by the will to live—what is it? Of what matter is it made? How can it be localised, how isolated, in what way may it be analysed?

As we have seen, all that can be got from a living organism are chemical compounds or structural elements, representing only more or less deformed products of life and the instruments which it has forged and used. This is not living matter, and as for the psyche, we cannot conceive a material or dynamic image of it.

Probably there are some who will find that these statements of mine are inspired by an excessive desire to criticise and will accuse me of forgetting that in science, as in other manifestations of life, it is important above all to act, while the speculations of criticism may at times hamper progress. From what I have said, however, the value of researches in chemistry and physico-chemistry for the advancement of biological knowledge is evident. I never opposed them; the idea would be absurd and in contradiction to the course of my life as an investigator. I have only sought to fix the limits within which physiological chemistry may be applied to the explanation of vital phenomena, and to point out that the facts which

it reveals are often the product of technical artefacts and therefore do not always deserve all the significance which has been attributed to them. I have likewise called the attention of scholars to the inconveniences and dangers of misleading terms.

One may also object that my statements are in great part the outcome of the most obvious finalism, and that for this reason I lay myself undefended to the charge of heresy towards the dogmas of a certain exclusive science which does not consider teleology as a scientific doctrine only because one can maintain that physics and chemistry have no need of it. Should we therefore exclude any teleological statement from biology as well? If it were only as an hypothesis of work, the conception of finality is as indispensable to the biologist as the atomic theory is to the chemist, perhaps even more so; for in many cases we should not know how to analyse the functions of an organ, nor be able to plan a rational series of experiments, without the dominant idea of revealing the contributions of the organ to the functional synergy of the being to which it belongs, namely, the aim it is made for.

I realise that I have treated the question of finality in a very summary manner. This question has spilled much ink and will spill more on the altars of biology. But I did not deem it necessary to spend myself on such a thorny argument, because I believe that in this, as in so many other more or less philosophical debates, it is often only a conflict between irreconcilable mental temperaments which cannot come to agreement. As well might one impose one's own taste in colours, sounds, flavours, or scents.

When I examine myself, my movements and conscious actions, and feel them inspired by an instinctive tendency towards individual or collective defence, making the best use of the means which lead to this end, when I consider that my whole organism represents a corporeal entity directing its conscious and unconscious acts towards the maintenance of the conditions necessary for the preservation

of nervous activity, I cannot really separate the so-called vegetative functions from the functions of relation and these from the psychical ones. I must recognise that my being represents the cumulative efforts of ages, co-ordinated by special tendencies for the attainment of a certain goal. With these tendencies it has been endowed by the chances of heredity and hands them on, a flaming and unquenchable torch, to its descendants. *Homo sum ; humani nihil a me alienum puto*. How is it possible not to be a finalist in biology, at least at the present time?

I would not venture to deny that perhaps in the far distant future we may be able to unify everything and link up the inorganic with the organic world. But while waiting for the messianic event, let us agree to follow the facts without being hampered by preconceived dogmas. Let us recognise that in living organisms, even leaving out of account the psychic processes, there are purposive actions towards objects near or remote. The phenomenon may be illusory, but inorganic matter does not present it.

Because physics is an older science, and, since its problems are simpler and less variable, has advanced further, is it necessary for biology to forgo its scientific claims if it cannot adapt all the phenomena which fall within its scope to the mechanical theories of physics?

"From a more advanced point of view," says a mathematician, a keen student of philosophy, "it appears that the theory of unification is founded on criteria which are too narrow and one-sided, for it accepts as perfect and general the most advanced type of science and requires too rigid subordination to it of the other forms of knowledge. Therefore the point of view of mechanistic philosophy is modified by the progress of biology which, reacting in its turn on physics, paves the way for the understanding of a better unification, *i.e.*, a more general and perfect type of science which includes the special sciences separated by technical exigencies." ¹³

Let us therefore investigate living beings without pre-

conceived ideas and dogmatic restrictions; they may thus reveal to us many facts which we were far from suspecting, or which we had never grasped because between them and us we had interposed the shield of our prejudices in favour of simplification and unification.¹⁴

Analogous reflections might be made with regard to the supposed factors of evolution, the doctrine which has ruled such a great part of modern thought. In allowing ourselves to be trammelled by the suggestion of a dominant idea, we should deserve the ironic reproof of Goethe :

“ Am Ende hängen wir doch ab
Von Kreaturen die wir machten.”

(“ The creatures which we strove to form
Enslave us makers, in the end.”)

Therefore I think it not superfluous to close these general considerations by expounding some doubts which among students and especially biologists should perhaps be more diffused.

The earth has not always harboured living beings. Of this we are confident, because, under the conditions prevailing in very remote ages, no chemical combination whatever could have existed, and, least of all, the carbon compounds which are characteristic of the animal and vegetable world to-day. We don't know how life appeared on our globe; experiment forbids the belief, at least for the present time, in spontaneous generation, that is, the creation of living beings from unliving matter, and there is no reason to suppose that it occurred in a remote past, although *a priori* the possibility cannot be denied. It has been supposed that the first germs of life were carried on to the earth through the sidereal spaces from some meteorite, or borne on the waves of solar irradiation; but, leaving out of account the grave objections to this hypothesis, even if one wished to accept it, the question of the origin of life would only be pushed a step farther back; it would not be solved.

There are some, on the other hand, who venture to affirm that life, like energy, has no beginning, that living beings have always existed on the earth and that instead of carbon, they used other compounds, those of silica and titanium, for example. A large proportion of what to-day is inorganic, they say, has had its origin in processes unfolded in living beings. The inorganic world depends on biological processes of plants and animals, as is shown by the zoogenetic and phytogenetic strata of the earth's crust, strata from which whole chains of mountains are formed. Only in the presence of germs or of living beings does inorganic matter become organic and organised, while we witness continually the transformation of organic and organised matter into inorganic. All this, it is claimed, is founded on the results of daily observation and experiment, so that rather than seek the origin of life, we should explore the beginning of all that is dead.

But ever abandoning these deductions, in regard to which I feel more perplexity than when faced with the most exaggerated transcendentalism, and recognising the impossibility of propounding any probable hypothesis on the origin of life on our globe, one may nevertheless attempt to establish what conditions have determined the multiplicity and diversity of living forms which we have learned to group in kingdoms, types, orders, and species.

Palæontological data which demonstrate the similarity of actual species to those which are ancient and extinct and the analysis of structure among groups of living or, for certain characters, of all living beings, suggest that all species are more or less directly related. Two arguments in favour of this genetic affinity have been put forward on insufficient objective grounds—first, the transmission to the offspring of acquired characters, and, secondly, for vertebrates in particular, a certain superficial resemblance between the stages of ontogenetic development and the different species. Thus the embryo would pass through stages reproducing, though not exactly, the characters

of the species which have preceded it. In support of the theory of hereditary transmission, numerous other arguments based on facts were brought forward. The chief of these was the persistence of rudimentary organs, which were and are still useful to primitive beings, but are of no appreciable service to the more advanced. The presence of allied forms in certain regions and yet other arguments were put forward. In the animal kingdom, with which we are especially concerned, when extinct forms are compared with those that are living, they may be represented in such a way as to form one or more ramifications of a genealogical tree. The trunk and main branches would correspond to primitive archetypes, the terminal twigs to the more complex forms either living or extinct. So it was thought that one can derive living beings from a common primordial form. From it, by a continuous succession of slight modifications which leave their imprint on the germ plasma throughout the centuries, the various species have come into being.

This theory of a slow evolution gave rise to two principal lines of thought. The first is represented by Lamarck, who attributed the supposed phylogenetic development to the transmission by heredity of variations acquired by organs through use or disuse in adaptation to their surroundings. The variations, although localised in the beginning, were said to influence the entire being, modifying it as a whole, owing to the interdependence of its various parts.

The second hypothesis is associated with the name of Darwin, although incorporating some of the conceptions of Lamarck. It was not especially concerned with the origin of individual variations like Lamarckism, merely admitting that they occur, and holds that, thanks to natural selection following on the struggle for existence, those forms survive which happen to be best fitted for the preservation of the individual and of the species. It cannot be demonstrated, however, that characters acquired during the brief cycle

of life of the individual are transmitted to the offspring, since, according to Weismann, changes in the somatic plasma cannot modify the germ-plasma. We cannot suppose that the portion of the organism which receives and transmits the imprint of heredity was any more susceptible to impressions in the past than it is at present. For these reasons, although the doctrine of evolution implies the premise that hereditary characters began by being acquired, the theory, which attributes to natural selection the chief influence in the determination and fixation of form, is the most widely accepted. But Darwinism, which was of the greatest value to morphology, first as an hypothesis of work, and secondly because it gave a scientific ideal to classification, shows daily the insufficiency of its simplifications, notwithstanding its numerous and worthy supporters. Such a theory, which would explain the origin of species by asserting the continuity of phylogenetic development, necessarily ends by breaking down the barriers which separate the different species. In reality, however, the fixed specific characters which distinguish them tend to become better defined, although this might be attributed to a progressive diminution in variability. It is undeniable, in any case, that at the present time individual variations oscillate between very narrow limits and are such that they never carry the animal beyond the boundaries fixed by the specific characters of the species. We discover these specific characters to be increasingly numerous and complex. Thus we learn to distinguish each species, not only by certain somatic characters which are directly tangible, but also and even more clearly by peculiar cytological, chemical and physical properties. These include, for example, the size of the cell, the form and number of the chromosomes, the chemical composition of the tissues and humors, and perhaps also their physical state, resulting from particular conditions of their colloidal aggregates. Let us say also that the cytological, chemical and physical characters are representative of a

given species and lead us to distinguish between this and that race much better than the gross somatic features on which zoologists ordinarily rely. How otherwise could one associate scientifically in the same species the dogs which populate the earth and establish fraternal relations between a Newfoundland and Pekinese, between a mastiff and a greyhound?

Even when account is taken of extinct species, intermediate or transitional forms are often lacking. These should nevertheless occur if the species represented the various stages of a continuous and progressive development. The same argument may be used with scientific men who would consider the innumerable families of living beings as derived from primitive forms, animated in the beginning by an impulse lasting till now as though by force of inertia. This impulse should have given origin to species in the past and should continue their formation; *i.e.*, it should determine the so-called phylogenetic development. As suggested by Hertwig in his "Allgemeine Biologie," the natural species, according to the theory of descent, should evolve continuously and progressively in the same way as the pluricellular organism develops by epigenesis from an egg—not as the sport of causality, but with the same inward necessity which in ontogenesis makes the blastula produce the gastrula.

I wish to repeat that all these genealogical theories do not stand sufficiently firm against the adamantine resistance of species. Experiments of cross-fertilisation and hybridisation by artificial selection, designed to demonstrate their variability, illustrate this point. The result of these researches was chiefly to confirm, define, and amplify the law which governs the transmission of hereditary characters, a law first revealed by the genius of Mendel in his admirable researches at Brünn. The work of Mendel and his followers allows us to predict to some extent, and therefore to produce, certain characters in the off-

spring, deducing them from those of the parents, and so to distinguish some of their causal factors.

We have not yet the remotest indication of the nature of the factors contained in the gametes or sex-cells. After fusion, they constitute a zygote, maintaining their properties intact by a process which Mendel called segregation. They may show themselves immediately as dominant or remain temporarily latent as recessive. It has also been possible to demonstrate that the effects of these factors depend, not only on the presence, but also on the absence of some of them, leaving, so to speak, a clear field for the remaining ones, and on their reciprocal influence. Thus hereditary characteristics, little by little, will be analysed into their factors. It is evident what incalculable advantage may be derived from this knowledge, especially when turned to the improvement of the species of plants and domestic animals, and, above all, in regard to man. Statistics of human beings are being collected which will throw light on certain numerical correlations in the transmission of normal and abnormal characters, physiological or pathological, somatic or functional.

Hence it becomes clear that, within limits, exceptional relations among the innumerable factors present in the zygote may eventually determine new biological types, although demonstrating still further the immutability of the determinants of hereditary characters and therefore the resistance of the species to modification. This theory is all the more suggestive when one considers the great plasticity shown by the individual in the brief period of his existence.

Even the devotees of the blind fatality of natural selection who believe that unadaptable creatures are always produced in larger numbers than the adaptable and are eliminated later, even the most orthodox followers of Darwinism must recognise that the changes, from the sum of which is derived phylogenetic lineage, are not fortuitous but happen according to fixed laws. It is held by some

that evolution is irreversible, that the possibilities of variation are becoming progressively reduced (negative orthogenesis) and that the influence of the intimate nature of the developing organism determines the direction of evolution (positive orthogenesis).¹⁵ So that selection would not be the result of a fate more blind than that of Greek tragedy, but would be ruled by laws which limit and direct it. The statements of the Darwinists are besides somewhat arbitrary, because the idea of a more or less casual selection as the cause of slow evolution in an obscure past necessarily lacks an objective foundation. And, in fact, the most enthusiastic supporters of the theory have never been able to witness the formation of a new species.

This phenomenon, although within very narrow limits, was said to have occurred a short time ago in certain plants in which sudden spontaneous changes were observed—the so-called mutations.¹⁶ As happens too often, these observations were given a general significance, and it was considered that evolution did not proceed, as was first believed, by the slow accumulation of slight variations, but rather by the sudden explosion of somatic changes. These were, however, probably prepared for by imperceptible reactions, whose effect was gradually to render the equilibrium of the organism more and more unstable. So that even in these cases one might have to do with the sudden revelation of the results of slow individual changes. Many biologists agreed on this way of regarding mutations. Under the dominant influence of the Mendelian idea, they denied the possibility of new biotypes being formed by selection and held that variations due to individual adaptation had no power to modify genotypical properties. So that for the supporters of phylogenetic evolution nothing would remain but to admit the mutations or special combinations of hereditary characters producing by chance a new organic equilibrium, living and fertile, which might be perpetuated in a new form of species, sub-species or race.

These facts and arguments should have cooled the ardour of the classic evolutionists; but this has not always happened. On the contrary, for example, certain minds imbued with the love of novelty exaggerated the revolutionary significance of mutation. They went so far as to proclaim that certain teratological events causing hereditary malformations were mutations and therefore of evolutionary value. One may suppose that political passion is not a stranger to the assertions of those who so readily apply to human society the data supplied by the study of the functions of the individual. They are anachronistic imitators of Menenius Agrippa. Likewise one cannot deny that the great success of the Darwinian theory was due in part to the reaction of many people, especially in England, against the persistent intrusion of theological criteria in scientific research. However that may be, it is indubitable that the objective foundations of the theory of mutation are extremely scanty and of uncertain interpretation; the more so that, up to now, the only undoubted examples of mutation have been observed in species recently imported into Europe. Therefore one cannot avoid the suspicion that it was a question of the outbreak of atavistic characters due perhaps to past hybridisation. We know nothing of the determinants, immediate or remote, of these changes, or even whether these causative reactions are mainly internal or chiefly located in the surroundings. For this reason it is at any rate premature to found on these observations a theory of the origin of species by sudden mutations.

What has been said above leads to the conclusion that hypotheses on the origin of species are an indication of our mental tendencies, rather than the synthetic result of facts incontrovertibly ascertained. Let us admit it without further preamble: the success attained by the theory of evolution of living beings on the earth is not due primarily to its self-evident character, for even the most generally admitted facts cannot always be reconciled with

it, but rather to the sympathy of the scientific world for the dogma of continuity of natural phenomena and therefore to the reluctance to consider the possibility of isolated formation. Some think: "If we were forced to admit this, why not recognise the divine Creator of Genesis?" With regard, then, to the factors of evolution, the mind of many biologists is set, so that they will not tolerate the discussion of any force which is not physical or chemical. And yet we ourselves are the cause of psychic phenomena which we do not know how to associate with those of energy, and a direct causal relation between chemical and physical energy and psychic force is inconceivable, and the immensity of our ignorance, when confronted with the very little that we know, does not authorise such dogmatic obstinacy in us. It would be more scientific to assume a humbler attitude and be less assertive in our formulæ.

We must, besides, recognise that the conception of genetic discontinuity of species and the theological dogma of their creation are not bound together by an imperative logic, and that this conception may even be reconciled with the general principle of evolution. In truth, he who does not know how to resign himself to a serene agnosticism on the causation of species would be able provisionally to satisfy his need for dogma by returning to the ancient conception of vital force. He would be able to postulate an agent analogous to will, which, using the matter collected on the surface of the earth (the erroneously termed biogenic elements), would mould mechanisms (the living beings). The agent would be revealed by means of organised forms which attain ever greater perfection and complexity. It could determine the various living species and modify some of them, as is seen in mutations, from previously constructed forms (and this would be reconciled with the general conception of evolution), while others would be left unchanged. The different results of its elaborations would constitute the groups which are

called species, differing in details, but resembling each other by the community of origin, more or less remote, which binds them together. Thus from the action, partly and necessarily uniform and only partly discontinuous, of this vital agent, would be derived those organisms capable of acts teleological in their appearance and which, when compared with our ego, are reputed conscious; organisms which, although resembling each other, could be divided into groups advancing progressively in complexity and relative perfection, so as to be capable of increasingly varied and complex reactions. Suitable offensive and defensive mechanisms are thereby rendered possible and partake more obviously of the character of conscious reactions. It is undeniable that the different types of organised beings, taken as a whole, show, with a few exceptions, the tendency to assume by gradual adaptations an internal structure, more and more constant. On the other hand, to increase receptivity and responsiveness, the sensory and motor apparatus becomes more and more differentiated. In order to attain this result, living creatures are obliged to pass through certain stages. Ontogenetic development confirms this; in development, especially the development of vertebrates, we see a summarised repetition, albeit a not very exact one, of the gradual transition from the simpler to the more complex forms, until is reached the final fixed design of the specific characters of the species.¹⁷

This representation of the facts of evolution seems arbitrary, to say the least of it, and looks like the figment of a fervid and unbridled imagination.

Nevertheless, let us not discount too far the rôle of imagination in scientific work. The eminent physicist, John Tyndall, shall speak for us. As everyone knows, he was also an admirable popular writer on science, clear and profound, as is often the case among men of science of the United Kingdom. The fragment I wish to quote is culled from a work in which are collected his lessons on

light. I read the book when a boy, together with others on heat and sound, in a French translation by Abbé Moigno, and I always remember the deep intellectual satisfaction and incentive they gave me. Works of this kind are of great service to science, not only for the knowledge spread abroad, but also for the fervent proselytes to science which they gain. Tyndall says :

“This conception of physical theory implies, as you perceive, the exercise of imagination. Do not be afraid of this word, which seems to render so many respectable people, both in the ranks of science and out of them, uncomfortable. That men in the ranks of science should feel thus, is, I think, a proof that they have suffered themselves to be misled by the popular definition of a great faculty instead of observing its operation in their own minds. Without imagination we cannot take a step beyond the bourne of the mere animal world, perhaps not even to the edge of this. But, in speaking thus of imagination, I do not mean a riotous power which deals capriciously with facts, but a well-ordered and disciplined power, whose sole function is to form conceptions which the intellect imperatively demands. Imagination thus exercised never really separates itself from the world of fact. This is the storehouse from which all its pictures are drawn; and the magic of its art consists, not in creating things anew, but in so changing the magnitude, position, and other relations of sensible things, as to render them fit for the requirements of the intellect in the sub-sensible world.”¹⁸

Methinks that the ideas on evolution set forth above will be considered as the product of an insufficiently disciplined imagination and therefore not comparable to that extolled by Tyndall. If one reflects that a piece of flint chipped in the shape of an arrow-head, or an axe of polished jade, or a potsherd, or a bone roughly fashioned like a weapon suffice for the investigator to assert that they are the work of a human will and that simply because these primitive objects reveal by their form that they were intended for a definite purpose, why not use

analogous arguments with regard to the structure and the teleological characters of living beings? They show a far more complicated mechanism adapted to multiple ends than that of the primitive weapons, which are attributed by us without the slightest hesitation to the will of our ancient progenitors.

But it may be objected that, whereas we know man and his works in different periods of his life on earth and that in certain savage tribes the Stone Age persists till now, and whereas we encounter in ourselves and our likes irrefutable proof of human will, the hypothetical agent, on the other hand, cosmic "Life" or "Will"—call it what you like—has never been revealed to us in any tangible way.

But we see the result of its action: should not this suffice? Outside our own ego, have we ever encountered a psychological fact which was directly tangible? And this notwithstanding, must we not recognise in living beings, at any rate in those most nearly related to us, the workings of consciousness?

It can also be brought against this theory that it is too obviously anthropomorphic, because, in reality, it is only a projection to the exterior of particular states of our own consciousness. But can we do otherwise? The same conception of energy which dominates all modern science and pervades so much of our scientific theories—is it not derived from the sense of effort, from the stimuli which the peripheral apparatus for voluntary movements sends to the brain, and from recollections of previous efforts which rule the actual impulses of the will? And our representations of space and time to which are united all the manifestations of our mental life—are they not certainly the result of special sensitive impressions, which have determined and which awaken special mnemonic images?

Let me recall to you the profound and ironical reflection of La Rochefoucauld: "*Je ne suis pas si convaincu de notre ignorance pour les choses qui sont et dont la raison*

nous est inconnue, que pour celles qui ne sont point et dont nous trouvons la raison." ("I am not so convinced of our ignorance of the things which are and of which the cause is unknown to us, as of those which are not and of which we find the cause.")

Undeniably, the theory of a "cosmic will" which moulds living beings, using some of the first made forms to create new ones, better and stronger in their adaptations for more numerous and varied ends (like the human will which made stages of progress from the sledge to the locomotive, from the catapult to the cannon), is not a working hypothesis, because from it we cannot deduce any line of thought which would lead to new experiments to confirm or refute it. Rather is it an act of faith which, although in masked fashion, makes us confess our ignorance on the origin of living beings and of their species, and gives us the illusion of having more nearly apprehended a supreme cause. It is an act of surrender, but a surrender of reason to sentiment which does not degrade, but exalts, because it is the natural consequence of our nature, wavering between sentiment and reason, which can only be at peace when it reconciles one with the other, merging them in the Divine Light which dazzles but comforts.

For the present, at any rate, we can only believe in it or resign ourselves to agnosticism.

And now if, in spite of the doubts, uncertainties, and deficiencies which I have shown in part, I dared ask: Does living matter exist, and if it exists, in what does it consist? I should answer: No, living matter does not exist in the ordinary sense of the expression; the chemical compounds and the structural elements of a living organism are in reality only the products of Life, the materials which it assumes, uses, and finally rejects. Living beings must be considered, in a given period, as mechanisms, permanent in outward form and intimate structure, but built up of temporary materials which pass through them in a more or less rapid flow. From this point of view they may be

roughly compared to a whirlpool, constant in shape, yet continually changing in substance, or to those plumes of cloud which are seen at times on a mountain crest beaten by a furious blast; notwithstanding the continuous and rapid transport of their contents, they maintain their size and form, because of the dominant action of the summit.

"L'être vivant," said Cuvier, "est un tourbillon à direction constante dans lequel la matière est moins essentielle que la forme." ("The living being is a whirlwind, constant in direction, in which matter is less essential than form.")

In the time which elapses between the entrance of suitable foodstuffs into the organism and their restitution more or less modified to the exterior, a small part of them serves for repair or building of structures. The greater part is used for energy requirements and for the maintenance of the physical conditions of the individual. Should we affirm that these substances or part of them have become alive during their sojourn in the organism, when they are burned to produce energy or when they are fixed as reserve food-stuffs or for building up tissues? In reality, organisms appear as if they were animated or enlivened with a will to live, a vitality directed towards a future development, always more intense, perfected, and conscious. The materials of which they are made show themselves as the basis of energy, or form the instruments for functional activity. And this will to live determines the most obscure functions of the lowliest tissues, and is likewise the basis of the loftiest manifestation of thought, fashions the shape of the flower, distils its perfume, and elaborates its colour, so that the bird and the insect are drawn unconsciously to fulfil their office of intermediary in fertilisation, and pushes the intellect of man towards the most general conceptions of the Universe.

Properly speaking, then, there is no living matter, but there are materials organised and utilised by the will to live.

CHAPTER III

ON SOME RELATIONS BETWEEN INHIBITION AND WILL

I WILL now speak of some old and recent experiments of mine which chiefly concern the nerve-centres of the marsh tortoise (*Emys europæa*). This harmless chelonian has exercised the minds of zoologists, who a dozen times or so have racked their brains to rename the creature. It has been successively labelled: *Testudo orbicularis*, Linnæus (1775); *Testudo europæa*, Schneider (1783); *Testudo meleagris*, Shaw (1789); *Testudo flava*, Daudin (1803); *Emys lutaria*, Schweigger (1814); *Emys europæa*, Schweigger (1814); *Testudo europæa*, Bojanus (1819); *Terrapene europæa*, Bell (1826); *Cistudo europæa*, Gray (1831); *Lutremys europæa*, Gray (1855); *Cistudo lutaria*, Strauch (1862); *Emys orbicularis*, Blanford (1867), and in all probability we are not done with it yet. I do not recall for what reason in 1883, when I began my researches on this animal, I chose the name of *Emys europæa*. It would have been better, in deference to the classic work of Bojanus,¹⁹ to have called it *Testudo europæa*. But now for forty years my colleagues, pupils, and myself have called this tortoise *Emys europæa*, and therefore I think it inopportune to change.

Emys europæa is well adapted for physiological investigations owing to the remarkable power of survival of its tissues, which can be kept isolated in the living condition even without using any particular artifice. For this reason it lends itself in a special way to experiments on the heart and its innervation, and to experiments on the nerve-

centres. This tortoise is widespread in its distribution and therefore easily procured; it lives in ponds, streams, lakes, marshes, and rice plantations. It is found in Southern and Central Europe and extends north as far as Prussia and Poland, east as far as Russia in Europe and Asia Minor and south as far as Algeria; it is not uncommon in Central France and in Japan, where it is the object of many pictorial representations and sculptures, especially in bronze. It is known besides, that, like other tortoises of considerable dimensions, *e.g.*, *Emys blandingi*, it belongs to the fauna of North America. Students of comparative psychology, who are ordinarily of not too critical a temperament (*vide* the horses of Elberfeld) do not deny to this animal a certain measure of intelligence; they tell of a tortoise who answered to the name of Augusta and showed affectionate recognition of her mistress. I am obliged to confess that I have never obtained any expression of civility from the hundreds of tortoises with whom I have been associated in scientific work; it is true, however, that my behaviour towards them was not such as to enlist their sympathy.

I do not understand why this fairly common tortoise, with tissues that withstand manipulation better perhaps than those of any other vertebrate, is not made use of more frequently by physiologists. In many cases, perhaps, we are loth to depart from tradition, wherefore we impose upon the frog the ungrateful rôle of victim in our researches. *A propos* of the frog, we may recall the words of Claude Bernard :

“Tous les animaux peuvent servir aux recherches physiologiques . . . mais s'il fallait tenir compte des services rendus à la science, la grenouille mériterait la première place. Aucun animal n'a servi à faire de plus grandes et de plus nombreuses découvertes sur tous les points de la science, et encore aujourd'hui sans la grenouille la physiologie serait impossible. Si la grenouille est, comme on l'a dit, le Job de la physiologie, c'est-à-dire l'animal le plus maltraité par l'expérimentateur, elle est

l'animal qui, sans contredit, s'est associé le plus directement à ses travaux et à sa gloire scientifique." ¹²

("All animals may be used in physiological research . . . but if we had to keep account of the services rendered to science, the frog would deserve the first place. No animal has assisted in the making of greater or more numerous discoveries in every department of the science, and still to-day, without the frog, physiology would be impossible. If the frog is as has been said, the Job of physiology, that is to say, the animal most ill-treated by the experimenter, it is, without question, the animal most directly associated with his work and with his scientific fame.")¹²

These words of Claude Bernard evoke in especial fashion the image of Galvani, when on an evening of September 1786 he stood intently observing the hind-legs of a frog hung by means of a hook to the balustrade of a terrace in his house in Bologna. And we ask ourselves with Gherardi, the illustrator of the works of the famous Italian, what other course would human progress have taken if the balusters, instead of iron, had been of wood or of stone.²⁰ Chance has always played a notable part in great discoveries, and this should render us less exacting in applying the unbending dictates of logic.

We may say at once that our tortoise will never boast the patents of nobility of the rival frog; it is nevertheless of ancient reputation among Italian investigators. Indeed, apart from the researches of Fontana and Rolando, there are the notable experiments of Francesco Redi, a Tuscan gentleman who lived in the second half of the seventeenth century.

Physician to the Grand Duke of Tuscany, a courtier of bizarre and independent spirit, poet and man of science, bold and sometimes penetrating, he was a typical representative of those unfortunate times when the power of the Medici was declining and the rulers were wavering between the traditional liberalism of the Tuscan people and acquiescence in the impositions of the Holy Office. In those

historical surroundings there still remained, though much weakened, the influence of the giants of the Renaissance who had irradiated so much truth and beauty over the civilised world; but the contemporaries of Ferdinand II and Cosmo III no longer possessed the mighty soul which was sublimated in Dante, in Leonardo, in Michelangelo — and the toleration of the martyrdom of Galileo has sadly concluded this glorious epoch.

Galileo had just died after nine years of retirement spent in great part in his villa at Arcetri, “il Gioiello,” where blindness took from him the only blessing which he could have enjoyed, that of looking from the windows of his dwelling on the rounded contours of the Florentine hills, extending in an exquisite harmony of line and colour.

Accused of heresy, threatened with excommunication, tortured not indeed in the body already enfeebled by age, illness, and the forced journey to Rome, but far more cruelly in the soul by the abjuration which he had been forced to sign with trembling hand, he stands out for all ages one of the noblest victims among those who have fought for the liberty of science. And perhaps remorse for this tragedy induced a brother of the Grand Duke, Leopoldo dei Medici, to consent to the request of a few followers of Galileo to found in Florence “l’Accademia del Cimento.” L’Accademia del Cimento carried the celebrated motto “provando e riprovando,” and had for a coat of arms three crucibles in an oven of fireproof clay surrounded by flames. The institution was called “del Cimento” because, as was written by Antinori ²¹:

“Those academicians, having rid their minds of all preconceived ideas, may retain or accept neither the opinions of others nor their own, if they are not confirmed in the crucible of experience.”

A propos of this, we have to remember that it is from Galileo, from Des Cartes, and from Leibnitz that the seventeenth century derived its attitude of speculation

and experiment, in the sense that all the doctrines which were put forward, and all the discoveries of that epoch, had their origin in the experimentalism of Galileo, in the analytical method of Des Cartes and in the intuition of Leibnitz. It is not too much to say that these three governing minds guided more or less directly those who in that epoch occupied themselves with science of nature or of mind.²²

In order to understand the academicians "del Cimento" it is necessary to remember that they were still under the direct influence of the great intellects who had preceded them in their own country, men endowed with clearness, with precision, with an unshakable vision of truth, and with an instinctive mistrust of generalisations. Guicciardini and Machiavelli were calumniated, especially the latter, because they dared to describe men as they too often are and not as people would have them be. For this reason we hold them to be the most truthful, impartial, and useful of the historians. And likewise in art, the Tuscans, with a marvellous work of selection, were always endeavouring to reproduce the truth; their Madonnas are natives of Siena or Florence, and the landscapes which surround them are exact reproductions of Tuscan scenery.²³ The same in literature, Dante, although imbued with mediæval theology, subordinated his divine poem to the laws of nature and penetrated the remotest depths of the human soul. And in science too the Tuscans were realists; they looked at natural facts with clear vision and without preconception. "Oh! how little we know; oh! how easy is it for us to go astray when we examine the things of nature and determine their most general proportions"²⁴—exclaimed Francesco Redi, the representative of biology together with Alfonso Borelli in the Accademia del Cimento.

These men, besides, were skilful artisans who knew how to work with their hands in metal or glass and to direct the task of the artificers associated with them. Visit the rooms in the Museo degli Istrumenti Antichi in Florence, where are

collected the instruments invented and made by Galileo, by Torricelli, and by so many others : see with what ability, having regard to the primitive means of those times, are constructed those thermometers, barometers, microscopes, telescopes, aerometers, those spheres demonstrating the permeability of metals, those hygrometers, those geodetic or geographic apparatus. The instruments have a peculiar beauty, for on them the years have spread the patina which clothes the things of the past ; which gives the lustre of bronze to terra-cotta, the iridescence of a bird of paradise to the commonest glass, which ennobles the form, softens the colours, rounds the contours ; the magical polish laid on by the hand of time, imparting to things, as to memories, a venerable lustre.

In truth, this digression is too long, but I could not resist the desire to recall to you that old Florentine School, the heirs of the experimentalism of Galileo, to which we owe remarkable observations and researches in morphology and physiology and whose thought we reflect more often than we are generally aware.

And now to return to our tortoise. We will begin by quoting the description which Redi gives of his investigations on the brain of this animal. He writes :

“ I endeavoured for my pastime to investigate some notions regarding the brain and the movement of animals. And for this end, having oft-times removed the brain from many species of fowl and quadrupeds and observed the results, the idea came to me to see what would happen with the terrestrial tortoise ; and in the beginning of November, taking one of these, I made a large aperture in the skull and removed the brain completely, cleaning out the cavity so that not even the minutest fragment remained. Afterwards I left the hole in the skull uncovered and released the tortoise ; and it behaved as if it had received no injury, walking without hesitation and going in whatever direction it pleased. The tortoise, which never lost the power of walking freely where it chose and of making any other movement, lived till May—a period of six months. When it was dead I examined the cavity from

which the brain was removed and found it clean and completely empty, except for a small black clot of blood. . . . Several other terrestrial tortoises survived whose brains were removed in like manner in the months of November, January, February, and March; with this difference, that while some moved away and went about at their pleasure, others, while they survived for a long time without the brain, did not move from the spot, although they might perform other movements. I have said that they lived for a long time because those who were least active remained alive for fifty days while others did not die for many months. It is not only the terrestrial tortoises who have this aptitude of surviving for a long time—and of moving about after being completely deprived of their brain, but this also happens with fresh-water tortoises: I have made the experiment with many of these, although they are not capable of so much resistance to injury, nor do they survive as long as the terrestrial kind.”²⁵

From this delightfully picturesque fragment of Redi it follows that lesions of the brain determine in terrestrial or marsh tortoises either incessant perambulation or complete immobility; but he did not push his curiosity to investigate the conditions which determine these apparently contradictory results.

“ Si en répétant une expérience ” (said Claude Bernard) “ on trouve des résultats discordants ou même contradictoires, on ne devra jamais admettre des exceptions ni des contradictions réelles, ce qui serait antiscientifique; on conclura uniquement et nécessairement à des différences de conditions dans les phénomènes, qu’on puisse ou qu’on ne puisse pas les expliquer actuellement.”¹²

(“ If on repeating an experiment the results are divergent or even contradictory, one must never allow that true exceptions or contradictions can exist, for this would be unscientific; one must simply and necessarily conclude that the conditions are different in the different phenomena, whether one can or cannot actually explain them.”)¹²

More than two centuries later, in the same Florentine School, I took up the researches of Redi and made clear the reason of his contradictory results.²⁶

As is well known, the brain of the tortoise is divided longitudinally into four segments indicating its embryonic developments and definitive morphological structure; that is to say, into hind-brain, mid-brain, intermediate and fore-brain. The hind-brain is represented by the myelencephalon or medulla oblongata or bulb and its appendages, and by the metencephalon or cerebellum.

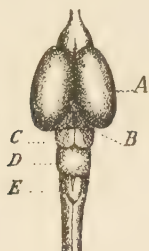


FIG. 2.—Encephalon of *Emys europæa* viewed from above.

A = telencephalon.
B = diencephalon.
C = mesencephalon.
D = metencephalon.
E = myelencephalon.

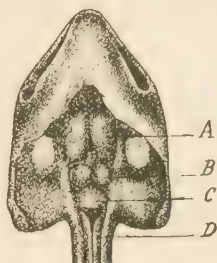


FIG. 3.—Brain of *Emys europæa* and its relations to the cranial cavity.

A = telencephalon.
B = mesencephalon.
C = metencephalon.
D = myelencephalon.



FIG. 4.—Encephalon of *Emys europæa* viewed from the side (Bojanus).

The mid-brain or mesencephalon or optic lobes consists of the dorsal part, the vault or *tectum mesencephali*, very important owing to its motor sensory connections, and of the ventral portion, or *tractus peduncularis*, which contains the paths of conduction and in particular the *tractus tectobulbaris et spinalis* which establishes relations directly or indirectly with the motor centres of the bulb and spinal cord. The diencephalon, intermediate brain, or optic thalamus, which comes next, although it

is the smallest of the cerebral segments, possesses a remarkable complexity of structure which varies in different classes of vertebrates. Finally we have the fore-brain, telencephalon or cerebral hemispheres including here the corpus striatum, and the olfactory lobes; and with regard to this last I may mention that there is an

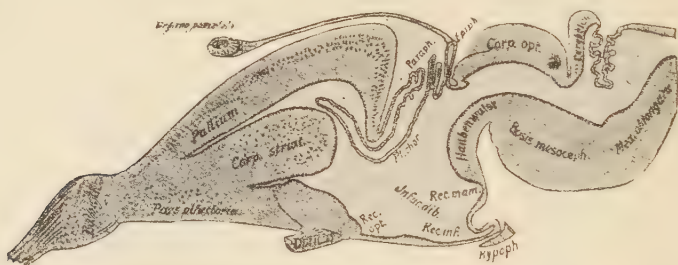


FIG. 5.—Encephalon of a reptile. Diagrammatic representation of a sagittal section (Edinger).



FIG. 6.—Longitudinal section of the encephalon of a reptile, *Varanus griseus* (Edinger).

important connecting bundle between the tectum mesencephali and the fore-brain. We must besides recognise in the brain of the tortoise a primitive neopallium, a forerunner of the hemispheres, the higher form of evolution of the nervous system which by increasing progressively in volume and complexity in mammals determines the dominant position of some of them,²⁷ (see Figs, 2, 3, and 4). In order better to illuminate the morphological relations of the

different segments of the encephalon I have figured two sagittal sections of a reptile brain (see Figs. 5 and 6).

According to my investigations the brain of a tortoise may be divided from the point of view of function into the same segments as when studied morphologically. When the brain, with the exception of the medulla, is completely extirpated (see Fig. 7) and this is done with special technique so that not a drop of blood is lost, the animal, a short time after the operation, walks about either continuously or periodically. It looks as if it is urged to move by uncontrollable stimuli because it does not stop whatever the obstacle which it meets. It may continue again and again to butt against the walls of the room until an accidental shifting of its position allows its progress to continue.



FIG. 7.—Encephalon of a bulbo-spinal tortoise. Beyond the bulb may be seen a short portion of the cervical cord. Even the cerebellum has been removed.

This perambulation is brought about by excessive movements, quite disproportionate to the result to be attained; and in fact while the normal animal in walking hardly lifts its plastron so that it seems almost to go trailing along the ground, the bulbo-spinal tortoise raises itself on its toes at each step and lets itself then fall heavily forward, making in this way a characteristic thud especially striking if the animal is placed on a wooden floor. To these animals the dictum of Montaigne may truly be applied: "Nous n'allons pas; on nous emporte."

It is easy to demonstrate that the perambulation described above is associated with integrity of the medulla oblongata and is not caused either by irritation of the bulb due to trauma or by irritation of stimuli from contiguous centres (*e.g.*, the respiratory centre); nor is it due to special conditions of the blood crisis and still less to external

stimuli. The stimuli provoking these movements should be therefore automatic, that is, they should be due to intrinsic conditions of the centres from which they emanate; they appear to be the external expression of nutritional alterations of that which we will call the ambulatory centre of the bulb. We may represent to ourselves schematically the rhythmic character of an automatic stimulus by analogy with a chemical reaction in which one may theoretically suppose the periodic formation of a determined substance.

Other characteristics are manifested by the bulbo-spinal animals. If during its progress it is violently shaken it does not immediately resume its perambulations but remains immobile for a period which may last up to twenty



FIG. 8.—Encephalon of a lobo-bulbo-spinal animal.

C = mesencephalon. *D* = metencephalon. *E* = myelencephalon.

minutes. In this case external stimuli not only do not provoke but even arrest the movements of progression.

When it is turned over on its back at first it remains still with head and limbs retracted into its carapace, but after a short time it tries to right itself, behaving like a normal tortoise, that is, it stretches its neck until its snout can act as a lever against the ground and with violent movements of its limbs rotates its body into the ordinary position.

Entirely different is the behaviour of tortoises which are left with optic lobes intact, that is to say, in which only the fore-brain and intermediate brain have been removed (see Fig. 8). In these conditions the animal, if not artificially stimulated, no longer moves. We can arrange the experiment in such a way as to record every movement and by this means we have established that it will remain motionless for weeks at a time.

The continuous movement of the bulbo-spinal tortoise

and the permanent immobility of the tortoise which possesses in addition the optic lobes (lobo-bulbo-spinal animal) leads us to suppose that these exercise a tonic inhibitory or arresting action on the special automatic centres of the bulb which determine perambulation and which we termed for the sake of brevity bulbar ambulatory centre. We know that the nervous centres may act not only to determine a movement, but also to moderate it or to stop it, and these inhibitory functions have a great importance in the determination of nervous activity, as we shall see later on.

The inhibitory action of the mid-brain, confirmed by other researches, is further shown when only the vault of the optic lobes is removed, the *tectum mesencephali*, leaving the rest of the brain intact (see Fig. 9). In this operation the portion of the mid-brain most rich in cellular elements is destroyed, but the connections between the fore- and hind-brain are not interrupted, since the lobar portion of the mid-brain, like the cerebellum, is not intercalated but super-imposed on the direct cerebro-spinal conduction paths represented by the *tractus peduncularis*. Incidentally I will remind you that we do not know of any long tracts in these animals with the exception of a slender thalamo-spinal bundle running down in the ventro-lateral column. The most obvious symptom in animals subjected to this operation is great restlessness and unusual liveliness. I put in a basket some normal tortoises and some others operated on as described above;



FIG. 9.—In this brain a hemisphere has been laid open to display the corpus striatum, the roof of the mesencephalon on the same side has been taken away so as to leave uncovered the cavity of the ventricle of the lobe.

whereas the former were nearly always in hiding and withdrawn into their shells, the operated ones were in constant movement, turning round and round in the basket and climbing up the sides in efforts to escape. If a normal tortoise is tapped during progression it withdraws head and limbs and retires hurriedly into its shell, remaining contracted in a state of passive defence for a long time; the operated animals, on the other hand, hasten onwards all the more, wagging their legs in a manner so free and nimble as to belie their proverbial laziness. The head is not retracted and their progress is not arrested by noise, luminous objects flashed into their eyes, or any other stimulus which would terrify a normal tortoise. If they are picked up they do not retire into their shells, but wriggle ceaselessly with great liveliness. A normal tortoise thrown into water dives at once to the bottom to hide in the mud or goes to conceal itself behind the leaves of water plants; a tortoise from whom the *tectum mesencephali* has been removed either floats quietly without swimming or swims very vigorously without showing the slightest tendency to take refuge or hide even when soundly beaten. It behaves, in fact, as if the impressions which reach it no longer evoked images of definite emotional states, such as would be present under analogous conditions in normal animals. And one notes that these apparent psychic defects are accompanied by a noticeable diminution of inhibitory powers shown, not only by the exuberant liveliness, but also by modifications in the time of reaction of reflexes (see Fig. 10). In point of fact this time is sensibly less in operated than in normal animals. Moreover if, after laying bare the *tectum mesencephali*, it is irritated by placing on it a crystal of common salt, one observes that the animal becomes much quieter and its reaction time is increased. Further, we note that in animals deprived of the vault of the optic lobes one cannot recognise the existence of sensory lesions. If there is a sense which should suffer from the effects of the operation

it is that of sight owing to the connection between the optic path and the mid-brain. But it is easy to show that tortoises after removal of the tectum mesencephali react to light stimuli in a manner which seems normal.

Extirpation of the cerebral hemispheres, if the optic thalamus or intermediate brain is left untouched, does not

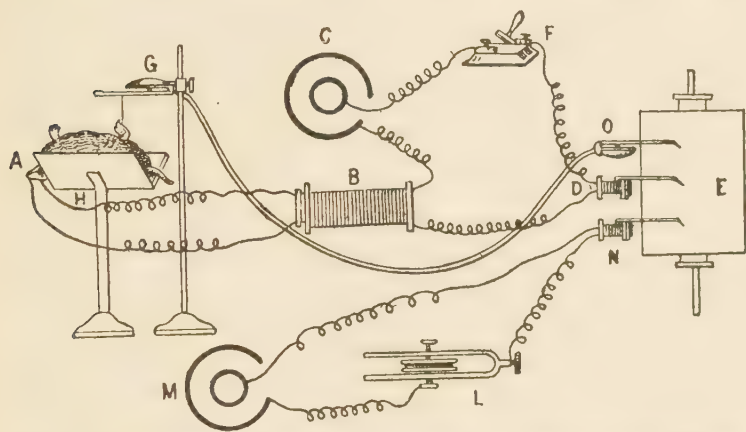


FIG. 10.—Apparatus for the determination of the reaction time of *Emys europaea*.

A, B, C, F, show the arrangements for applying faradic stimulus to the palate of the animal. By means of an electromagnetic signal, D, the moment of stimulation is registered on a revolving cylinder, E.

G, O, show the pneumatic arrangement by which the motor reaction of a hind limb is recorded on the same cylinder.

L, M, N, register the vibrations of a tuning-fork of 50 double vibrations per second and the exact rate of the cylinder, from which can be ascertained the time which intervenes between the stimulus and the motor response.

take away completely from the animal, at any rate in appearance, any of the functions which we attribute to the higher part of the brain. To all appearances it performs voluntary movements and it reacts adequately to stimuli. It behaves therefore like a tortoise whose brain is intact but its movements are slower and more uncertain. Were it permissible to apply a scale of comparison to the rudimentary intelligences of tortoises, I should say that those lacking hemispheres are more stupid than the normal ones.

There is another way of investigating the respective contributions to voluntary movement of the hemispheres and the optic thalamus. If the cerebral hemispheres are stimulated with a faradic current for thirty seconds the animal, after a latent period which may last a minute, performs movements of progression which cannot be arrested in any way and which continue even when it is lifted off the ground; after a few minutes of agitated motion it quiets down and resumes its habitual immobility. The same stimulus applied to the optic thalamus of a tortoise from which the hemispheres have been removed is not always attended by any result and when, after a longer latent period, movements occur, they are more feeble and of less duration than those which are seen following stimulation of the cerebral hemispheres. If this stimulation is applied to animals which have undergone extirpation of the *tectum mesencephali* it is easy to observe that they react with movements of progression which are more vigorous and last longer.

Although for various reasons, summarised above, it cannot be held that the movements of the bulbo-spinal and the immobility of the lobo-bulbo-spinal animal are due to irritation following operative trauma, nevertheless I wished completely to eliminate this objection by substituting for excision the action of some drugs causing paralysis and of cold. These methods have the further advantage that, when used with proper precautions, they allow us to observe the return to the normal, thus giving reversible effects. This, of course, is not possible with extirpation.* ²⁸

The poisons used were cocaine and stovaine. They were applied to the exposed segments of the brain either in crystalline form or by means of minute discs of blotting paper which had been soaked in solutions of the drug. To obtain a local action with cold we adopted a small metal receptacle shaped like a truncated cone, open at the base

* These investigations were performed in collaboration with my assistant, Dr. Zampa.

and closed at the apex, furnished with a small handle and containing ethyl chloride. The apex of the receptacle which was applied to the brain segment to be paralysed, had a diameter of 1.5 mm. or of 3 mm., according to whether one wished a larger or a smaller area exposed to the action of cold. The results of experiments with these two methods confirmed those obtained by total or partial extirpation of the various regions of the brain described above. From some points of view these experiments gave a better demonstration because by means of drugs and cold it was possible, besides abolishing function completely, to diminish the activity of the different brain segments, and also, as has been said, to observe the gradual restoration of normal functions. In the most recent series of experiments, we poisoned the animals with subcutaneous injections of strychnine and morphine, substances which respectively increase or diminish excitability. In this way, we were able to throw light on the relation between excitability and automatic movement. We showed still more clearly the automatic nature of perambulatory movements of bulbar origin, and also the extent to which changes in its excitability diminish or arrest them. But we shall treat of this more fully in a later chapter when we examine in detail the relations between excitability and automatism.

CHAPTER IV

ON FURTHER RELATIONS BETWEEN INHIBITION AND WILL

THE effects following extirpation of the different segments of the brain, described in the last chapter, were studied by me on other animals besides *Emys europæa*; the amphibians used were *Bufo vulgaris*, *Rana esculenta*, *Triton cristatus*; the sauria were *Champsia lucius*, *Lacerta viridis*, *Platydictylus mauritanus*; the ophidia—*Tropidonotus natrix*. But only the toad gave results as definite as those obtained with *Emys europæa*, and I have reason to believe that, as in the tortoise, it is its low excitability which makes it withstand the brain injury necessary to the experiment without serious irritation or shock. This fact bears out what has been indicated above on the relations between excitability and automatism, of which, as already said, I will treat later.

I could bring forward other suggestive facts regarding the course of the conduction paths for impulses controlling movements of adduction and abduction in *Emys europæa*, but I will refer those who seek fuller information to my paper on the subject. I cannot, however, forbear recalling my investigations on the reflex movements of the same tortoise. They showed that there were periodical variations either in the time of reaction or in the amplitude of the motor response. Since the stimulus is uniform and is repeated at intervals whose frequency is always the same, these variations obviously depend on changes in excitability and conduction in the spinal mechanisms, due to the action of the medulla oblongata which, in its turn, is

influenced by the higher cerebral centres, as shown in the experiments on the ambulatory centre of the bulb. In fact, the variations diminish when, after ablation of the fore-brain or intermediate brain, free scope is given to the inhibitory action of the optic lobes, and increase when ablation of the mid-brain removes all restraint on bulbar action. They disappear almost completely after section of the cervical cord. These facts may be interpreted as the result of stimuli which the brain sends to spinal centres, stimuli incapable of themselves of determining movements, but sufficient to lower periodically the threshold of excitability and therefore to raise the liminal value of external stimuli. In this way, the stimuli which eventually reach the animal are rendered extremely efficacious. The same stimuli at other times would not determine any movement or only feeble motor reactions.

These variations of excitability and conduction are more obvious in the fore- than in the hind-limbs, and this may be explained by the fact that the cervical spinal centres are nearer to the brain than the lumbar.²⁹ This suggestion is supported by an observation made in my laboratory on the dog which showed a reaction time longer for the fore-limbs than for the hind-limbs.³⁰ When the prefrontal lobes are removed, the difference becomes very much less, owing to an acceleration of the reaction time in the fore-limbs. Extirpation of the occipital lobes has the same effect, but in a less degree; ablation of the motor area gives negative results.

Besides studying the effects of destruction of the cortex, I investigated those due to its stimulation. I determined simultaneously the reaction time and the amplitude, measured graphically, of the motor response in an experimentally provoked reflex. When a prefrontal lobe is stimulated with a faradic current rather stronger than that used to obtain the ordinary effects in the motor region, one often sees a definite diminution of the amplitude of the myographic curve accompanied by an increase, sometimes

considerable, in the reaction time. These phenomena are clearly marked as regards the anterior limbs, and can hardly be made out in the posterior. They are of greater intensity on the contralateral than on the homolateral side, and persist several minutes after cessation of the stimulus. Stimulation of the occipital lobe gives very variable results which deserve careful examination; at times, however, the inhibitory effect is evident, although less intense than that obtained by stimulation of the prefrontal lobes.

From these investigations, therefore, it follows that some regions of the cerebral cortex, especially the frontal lobes, exercise an inhibitory action on the centres of the spinal cord, delaying and weakening their motor reactions; their influence is less proportionally to the distance of the affected segment from the encephalon. This is in agreement with the fact noted above that the reaction time is longer for the fore- than for the hind-limbs. As a consequence of these observations, can we not, from the relations of the reaction times of the scapular and pelvic limbs, deduce a quotient which will express numerically the intensity of the inhibitory tonus exercised by the cerebral cortex on the spinal centres? And might not this quotient serve as an index to graduate certain cerebral capacities and to compare individuals among themselves in this respect? Without making any dogmatic localisation of mental capacity, it is nevertheless suggestive that inhibitory powers are shown to exist chiefly in the frontal lobes. The power of inhibition has a large share in determining the functional basis of psychic phenomena. It is influenced by education and habit more certainly than any other cerebral manifestation and, to a great extent, moulds the intellectual and moral character of an individual.

In mammals, the more developed the frontal lobes the greater the intelligence shown. In man, they have reached a development far superior to that of animals, and this is commensurate with the superiority of his intellectual and volitional capacity.

But let us return to the researches on the brain of the marsh tortoise; we will endeavour to synthesize and explain the most salient results.

These experiments show that the animal whose brain is intact moves according to circumstances or, as one may say, when it wills; on the contrary, if the hemispheres and thalamus are removed, it remains immobile; after ablation of the optic lobes, it is in a state of agitation, either continuous or for periods of variable frequency and duration. The agitation however is independent of internal and external conditions and the movements are obviously excessive.

Trying to interpret these results, we are led to the following conclusion:—

The continuous or periodic perambulation of the bulbo-spinal animal is due to automatic impulses which emanate from the bulb and are transmitted to the motor mechanism of the spinal cord; on this mechanism the mid-brain exercises an inhibitory action which may amount to complete neutralisation, as happens in the lobo-bulbo-spinal tortoise. This functional relation between the mid- and hind-brains leads us to suppose that the fore-brain and intermediate brain determine voluntary action by attenuating more or less, according to the nature and intensity of the movement required, some of the various inhibitory actions exerted tonically by the mid-brain. In this way, that part of the bulbar automatism, which serves to provoke the particular activity of the given spinal centres, is freed. The voluntary act in this case would be the result of inhibition exercised by the cerebral hemispheres and optic thalamus on that which the optic lobes in their turn impose on the centres of the medulla oblongata. Certain bulbar impulses are thus liberated and sent far down the spinal paths (congenital or acquired) which conduct to the terminal centres of the movement required. The encephalic apparatus could thus be very schematically represented, with regard to its capacity for determining voluntary movement,

by a clock. The automatic property of the bulb would be comparable to the mainspring; the mid-brain to the escapement; the fore-brain to the pendulum which releases the anchor and distributes in a definite time the energy accumulated by nutritional activity or by the spring. The pendulum, however, has not uniform oscillations, but is controlled by internal and external stimuli in such a way that the mechanical reactions correspond with physiological needs.

The meaning of these complicated inhibitory processes becomes clear when the behaviour of tortoises, in whom the dorsal portion of the optic lobes has been removed or paralysed by cocaine, stovaine, or cold, is considered. As has been said, they react to stimuli with rapid and excessive movements which do not represent an emotional state, since they do not express defensive instincts which would be seen under the same conditions in normal animals. Their behaviour in this special condition and in that which follows stimulation of the mid-brain suggests that the inhibitory action of this part of the brain is one of the physiological factors conditioning psychic phenomena. So the lobar inhibition, by retarding within the ambit of the brain the speed of messages coming from the receptors should form a necessary part of the physiological basis of perception and memory. Perhaps it is in order to correspond to these psychic functional needs (that is, to make the final movement preceded by a state of consciousness giving the illusion of a reasoned choice), that the voluntary act, even in its centrifugal phase, is the resultant of a series of inhibitions.

Therefore, it would seem that, in consequence of the inhibitory mechanism, revealed by the researches described above, the final impulse which releases a voluntary movement is preceded and accompanied by the evoking of mnemonic images, which give to the will the character of proceeding according to a reasoned motive and an appearance of choice. If one would venture here on another

analogy even more schematic than that of the clock and corresponding even less with the nature of the facts we are discussing, one might say that just as the resistance interposed in a circuit may give evidence by light or heat of the electricity which traverses it, the consciousness which accompanies the movements brought about by the will is partly at least the result of inhibitions exercised by the mid-brain in the encephalic ambit.

I would not venture to affirm that it is only through this process of successive central inhibitions that the voluntary acts of the tortoise are brought about; the more so because, although no direct paths between the fore-brain and spinal cord are known, there are a few slender thalamo-spinal connections in these animals.³¹ But neither would I affirm that the existence of important long tracts in higher animals excludes the possibility of a series of analogous inhibitions developing in their brain to determine a voluntary act. We know in effect what numerous concatenations of neurons precede the terminal path of a voluntary impulse and the important contribution of antagonistic muscles to the accomplishment of a given voluntary movement.

It is in the elementary form of a function that one should, whenever possible, seek its essential foundations. So I believe, as I tried to show in the first chapter, that the study of humoral relations may throw light on the mechanism of transmission of neuro-motor impulses, at any rate in their terminal phase. Plants obviously manufacture motor power in the most rudimentary manner. Their movements indeed, and especially the circumnutation so ably studied by Darwin,³² are the direct mechanical expression of the nutritive cycle of certain groups of cells—are, in other words, elementary classic examples of automatic actions analogous to those recognised in a much complicated form in the bulbar centres.

But Darwin also showed that external stimuli may modify these movements of circumnutation adapting them to the

requirements of the surroundings. It is as well to recall his own words on the subject. The great naturalist says :—

“ Why every part of a plant whilst it is growing, and in some cases after growth has ceased, should have its cells rendered more turgescient and its cell-walls more extensile first on one side and then on the other, thus inducing circumnutation, is not known.”

And further on he adds :—

“ Circumnutation is of paramount importance in the life of every plant ; for it is through its modification that many highly beneficial or necessary movements have been acquired. When light strikes one side of a plant, or light changes into darkness, or when gravitation acts on a displaced part, the plant is enabled in some unknown manner to increase the always varying turgescence of the cells on one side ; so that the ordinary circumnutating movement is modified, and the part bends either to or from the exciting cause ; or it may occupy a new position, as in the so-called sleep of leaves. The influence which modifies circumnutation may be transmitted from one part to another. Innate or constitutional changes, independently of any external agency, often modify the circumnutating movements at particular periods of the life of the plant.” *

Truly one could not describe more clearly the relations between automatism and excitability. And in fact Darwin speaks of organs which, while they move by intrinsic changes, may also react to external stimuli, using with appropriate modifications the automatic movements indicated above. This would correspond with what I have suggested as regards the voluntary acts of *Emys europæa*, which are the result of automatic activity of the bulb modified in different ways by stimuli from the receptors. So the effect should be attained by delivering inhibitory influences in the highest part of the brain and, by so doing, bringing into play, together with movements, psychic and mnemonic phenomena.

* Darwin, “ The Movements of Plants,” London, 1880, p. 546.

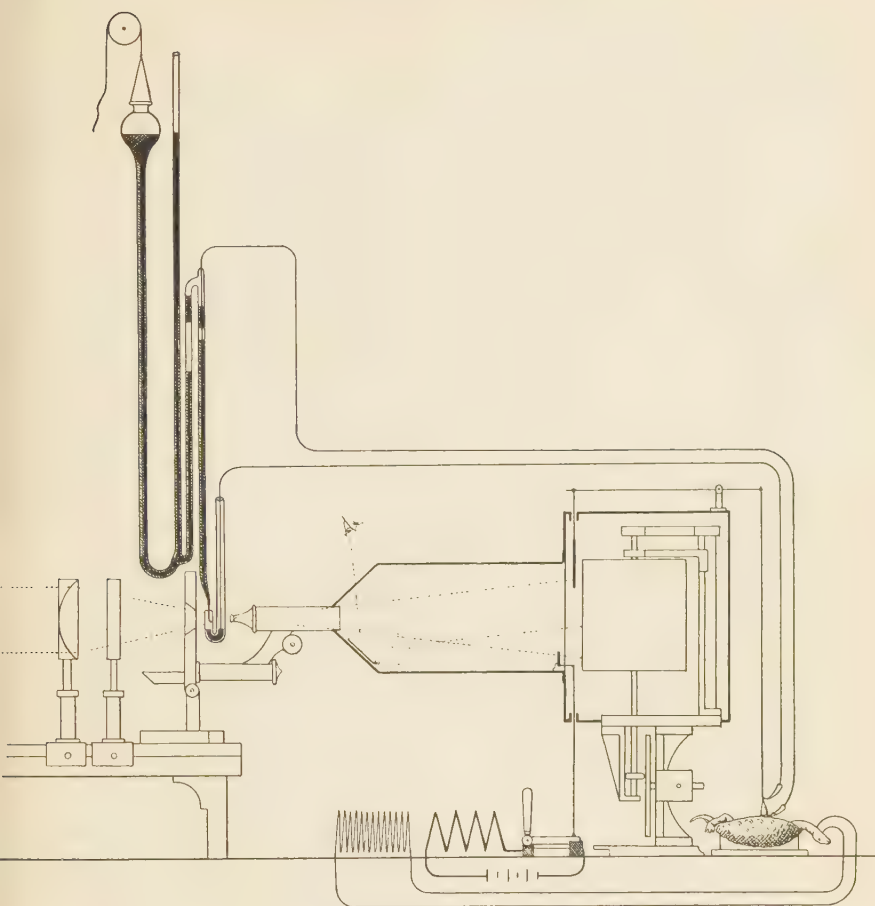


FIG. 11.—Apparatus for simultaneous record on the same tracing of the electrical and mechanical rhythms of the heart and of a faradic stimulus applied to the vagus in *Emys europæa*.

The chief points of this electrical arrangement are :—

A capillary electrometer in connection with two non-polarisable electrodes, supported on the apex and base respectively of a beating cardiac auricle.

A microscope which projects a magnified image of the fibre which corresponds to the end of the column of mercury.

A lever which receives and magnifies the mechanical rhythm. A little black lever which, by its rise or fall, shows the duration of the vagal stimulus.

A revolving cylinder, with photographic paper enclosed in a box provided with a slit by means of which the above mentioned experimental findings can be registered.

Since we are obliged to admit that these are allied to permanent changes in the higher nervous centres, we may once more call attention to the relations postulated between inhibition and assimilation or anabolism, in contrast to the manifestations of excitability associated with a release of energy which are undoubtedly disassimilative or katabolic.

I would willingly recall the attempts made to represent inhibition as the result of intensive anabolic function, because I lent some support to this theory, not only by my researches on the brain centres, just recorded, but also by those on modifications of the electric rhythm of the heart following stimulation of the vagus.³³ The mechanical rhythm of the heart was registered photographically by means of a lever; for recording the electrical rhythm, the capillary electrometer was used, the non-polarisable electrodes being placed one at the base and one at the apex of the beating heart (see Fig. 11). The results obtained were recently confirmed by one of my pupils and myself, using a string galvanometer to record the electric changes. In these experiments, performed on the heart of the marsh tortoise, isolated except for its nervous connections, which were kept intact, I observed that when the vagus was stimulated so as to render the cardiac contractions less frequent and ample, there was at the same time a considerable diminution in the negative phase in the electric rhythm, and a large increase in the positive phase (see Fig. 12).

Gaskell,³⁴ in experiments which were technically different, but carried out also on the isolated heart, had obtained results analogous to mine, and he and I, in conformity with the theory of Hering, agreed in attributing the inversion of the electric rhythm to increased assimilative processes following stimulation of the vagus and associated with inhibition of the heart. Our reasoning was simple; mayhap it was even too simple: If, as is thought, any increase in katabolic activity is accompanied by an increment in the negative phase, should one not interpret the

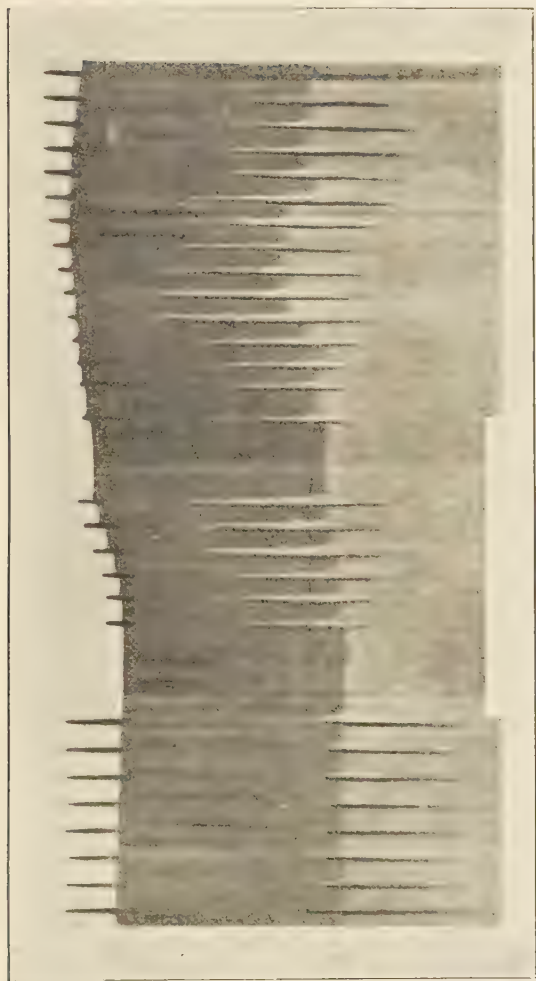


FIG. 12.—Tracing of the mechanical and electric rhythms of a cardiac chamber of *Enys europaea*.

C = cinematogram. E = electrocardiogram.

During the faradisation of the vagus, indicated by the indentation in the lower border of the figure, there can be seen:—a decrease in amplitude and rate of the mechanical rhythm, showing the inhibitory action of some fibres of this nerve; an inversion in the phases in the electric rhythm; a decrease in the negative (descending) phase, and an increase in the positive (ascending) phase; the appearance of an oscillation of tonus which shows the positive tonotropic action of some fibres of the vagus.

opposite phenomenon, *i.e.*, increase of the positive phase, as a symptom of intensified assimilation? The facts observed by Gaskell and myself might perhaps be differently interpreted, but although this doubt has crept into my mind, I do not believe as yet in abandoning our theory without further evidence.

Certain considerations point to a relation between assimilation processes, the inhibitory action of the vagus, and the presence of potassium salts. While working on this subject in my laboratory,³⁵ a pupil of mine observed that, by raising the content of potassium salts in the perfusing fluid of an isolated heart, the latter showed increased powers of assimilation. It was then found that the inhibitory action of the vagus only appeared when potassium salts were present. Let me recall that, as early as 1882, in a work³⁶ in which I suggested a polymerising action of the red blood-corpuscles on peptones, I attributed this result to the potassium salts present in these cells, reasserting Pouchet's statement :—

“Certains sels de potassium agissent comme déshydratants, ce qui n'a pas lieu pour les sels de sodium (Michael et A. Kopp). Lieben a fait voir que l'aldéhyde ordinaire se déshydrate en présence du formiate de potassium. Dans les végétaux chez lesquels les actions de déshydratation sont prédominantes, la potasse l'emporte en quantité sur la soude; et peut-être pourrait-on regarder, en considérant sa forte proportion de sels de potassium, le globule sanguin comme le *primum movens* des actes de déshydratation donnant lieu, dans l'organisme animal, aux formations synthétiques. Les globules rouges représenteraient ainsi, en quelque sorte, le côté *végétatif* de l'organisme animal.”³⁷

(“Certain potassium salts act as dehydrating agents, which is not the case for the salts of sodium (Michael and A. Kopp). Lieben has shown that ordinary aldehyde is dehydrated in the presence of potassium formiate. In plants in which dehydration reactions predominate, potassium is present in greater quantity than sodium; and perhaps, considering the large proportion of potassium salts which it contains, one might regard the red corpuscle

as the *primum movens* of the processes of dehydration, giving rise, in the animal body, to the formation of synthetic products. The red corpuscles would thus in some way represent the *vegetative* aspect of the animal organism.”³⁷

The subject of the action of salts, their qualitative and quantitative relations in the fluids of the body and in seawater, the influence of their respective anions and cations, their rapidity of migration, their electric potential, their radioactivity and other properties besides, is one of the most attractive problems of recent physiology. But it would carry me too far, and I must limit myself to this brief outline. I will only point out that, according to recent investigations, the peculiar physiological activity of potassium should be attributed, not so much to its specific properties as an element, but rather to its radioactivity. It may, in fact, be replaced by another radioactive element, provided the latter is dissolved in the circulating fluid in such proportion as to produce the same number of radiations as potassium itself, *i.e.*, so as to be equi-radioactive with it. Analogous observations were made, not only as regards cardiac inhibition, but also on other functions—as, for example, the permeability of the capillary endothelium and that of the epithelium in the glomeruli of the kidney.

The study of inhibitory processes, central and peripheral, has shown their widespread use and their efficacy in controlling the functions of living beings. I have called attention to central and peripheral inhibitions controlling voluntary acts, which, depending on complicated interrelations in the brain, are manifested peripherally, not only by the contraction of certain muscular groups, but also by the simultaneous inhibition of tone in their antagonists. There is also the example of the inhibitory action of the vagus on the heart. Many other moderating influences, and processes of arrest might be cited. These depend on combined humoral and nervous actions, as do numerous other phenomena of life. It will be understood that,

owing to the importance of the subject, a great many theories have been put forward to explain the mechanism of inhibition, besides that given above, which we may call the assimilative theory. To discuss them would take too long and would be tedious; one may concede that in all or in many of them there is an element of truth, at any rate in some cases. It is improbable that all inhibitions are determined in the same way and, especially in vital processes, it would be a mistake to be too rigid in our theoretical explanations. As regards the results of my investigations on the brain of the tortoise, I cannot agree with those who deny that the phenomena are due to inhibition and attribute them to a condition of decerebrate rigidity. In that case, one would have to discount the results obtained, not only with experiments involving destruction of the brain, but also those of experiments carried out by means of drugs and cold.³⁸

To the inhibitory effects derived from combined humoral and nervous action, we may add those resulting from the intimate connections which link the cells together. A classic example is shown during embryonic development. The fertilised egg of the triton, left to itself under favourable conditions, gives rise to a single embryo. The egg-cell divides into two blastomeres, the blastomeres into four, and so on by geometrical progression. This division is accompanied later by differentiation and polymerisation of the elements to form tissues, organs, and various sorts of apparatus in the organism progressing during ontogenetic development. But if the two primary blastomeres become separated one from the other, it happens, as was discovered by a pupil of mine in my laboratory, that each gives origin to a complete embryo. This fact leads us to consider blastomeres, at all events the primitive blastomeres, as totipotent, *i.e.*, endowed with equipotent building capacity, which is apparent when they are isolated. When, however, as in normal conditions, each can act on the other, reciprocal stimulating and inhibitory influences

impel each of the blastomeres and their offspring to produce half an embryo with those differences that distinguish one half from the other.³⁹

Notwithstanding many and various digressions, I think I have not wandered too far from the principal theme—the study of certain relations between inhibition and will. I have spoken almost exclusively of some of my investigations, but I have done so in order to call attention above all to results which might lead to further researches on the central determining causes of voluntary acts. This is one of the most interesting subjects in physiology even when, as in *Emys europæa*, it is studied in rudimentary form.

The will, understood in its widest sense, is undeniably the highest function of living beings, because it reveals itself as the loftiest expression of nervous activity, based on the essence of intense but unconscious life of all organised beings. In truth, indisputable evidence of voluntary acts is only seen in higher animals and especially in man. They constitute his greatest privilege, that which really determines the incommensurable superiority of the human race over all living beings, even over the anthropoids which in other ways show so many features similar to his. The will of which we are so proud, because it legitimatises and exalts our actions by the consciousness, apparent at least, of motives and aims immediate and future and by the appearance of spontaneity, has made of man a sovereign power which subordinates to its needs and to its passions the forces of nature and all other living beings. It impels him, moreover, to examine the origin and end of all that surrounds him with the hope or illusion of one day penetrating the mysteries of cosmic energy, whence arise the energetic harmonies of the universe, the formative dynamism of living beings.

The will, moreover, with progressive improvements, has succeeded in constructing mechanisms which, although possessing nothing in common with organic structures,

serve as accessory organs, enhancing his capacity for life and power.

The will has not merely supplied man with powerful engines which increase kinetic energy; it has also armed his senses. Instruments allow his vision to roam across immense spaces; they bring the infinitely little to his ken. They carry to him sounds from afar off or assist him to relive events which happened in the past.

The human species, and especially its brain, seems indeed—and I like to repeat it—the *chef-d'œuvre* of life on earth.⁴⁰

And in truth, by comparison with what can be imagined possible in other animals, do not the ethical, æsthetic, and utilitarian ideals of man reach a height that is almost incommensurable? In what other being does the problem of the origin and end of life impress itself in mystic or scientific form as on the human mind, forming one of the most efficacious and, in many cases, the principal motive of his conscious acts? Has not man, by means of verbal and graphic symbols of his thought, added indefinitely to the ideational and effective potentiality of the individual and of the species, and rendered permanent the record of every event, making of the idea a stimulus independent of time and space? Does he not brave the frozen regions and the unexplored summits, only to prove his superior will even where nature tolerates scarcely any other form of life? Has he not become by sapient artifice the fastest and most powerful courser of the earth, the most vigorous and daring plougher of the ocean? And does he not contend in aviation with the most resistant and hardy denizens of the air? Has he not silenced pain and learnt how to combat wisely the wiles of minute beings which lie constantly in wait for his life, can he not arm himself scientifically against the toxins elaborated by these microscopic adversaries?

All the other organised and living beings together have never consciously and voluntarily completed any kind of

work comparable to the individual or collective progressive actions of humanity.

The inventions and powers won by human will are transmitted from man to man, from one generation to its successors, and developing progressively, become fixed as the ideal and the practical patrimony of humanity. Human will has raised itself to such eminence, chiefly because with the spoken and written word it has created phonetic and graphic symbols which allow the communication between individuals of the results of their observations, researches, and intuitions. Thus the conquests of single individuals, associated and co-ordinated, became the patrimony of any human group and thus, from generation to generation, the results gained by individuals in the fields of ethics, æsthetics, and science became the common property of all.

This capacity of the human will to perpetuate in the species the united achievements of individuals appears, in the actual state of our knowledge, as a privileged condition with respect to the other functions of living beings. For, notwithstanding the lively desire of biologists to be able to demonstrate the transmission to the offspring of characters acquired by an individual through accidental circumstances, internal or external, and thus to surprise a factor of the evolution in action, one must admit that the inheritance of individual variations is still a matter of lively discussion. Of so much the greater importance then appears the constant transmission of mental acquirements, which, like instruction, cognition, and ideas, increases the power of man among his contemporaries and descendants. It is a transmission of mental characters, and the germinal cells do not take part in this process of evolution, nor is this power transmitted by a single individual, but collectively. The difference between it and the inheritance of acquired characters is therefore fundamental. But this does not prevent—I like to insist on it—the conquests made by the human will, just for their property of being

transmissible in whatever way, to have a highly privileged position with respect to all other organic functions, which do not possess their property of expansion or their capacity for propaganda.

So that, in man, conscious life, and the will which is derived from it and is its external manifestation, assume an intensity, variety, and depth which have no precedent in the world of creatures, which make of man a being capable of forging himself weapons of defence and of individual and collective dominion, making of him a geological factor of unsurpassed importance.

Whereas unconscious as well as conscious acts are especially directed in all animals to the same end of defence of the integrity of the individual and of the species; in man, on the other hand, many conscious actions, individual and collective, seem to be performed for the attainment of much more remote effects, that is, for harnessing to his service energy, whether of inorganic, organic or living origin, for the elevation of humanity, for the progressive dominion of man over nature. We must, however, recognise that the instruments which man makes for himself to help him in his struggle for defence and dominion, although they may be of great power, appear rough and primitive when compared with the structures shaped by unconscious life, mechanisms so subtle that the most powerful magnification is not enough for their analysis, and so appropriate as to be a constant model of action and beauty. Between the manifestations of unconscious life and those of human will there is ever an infinite distance, immensely greater than that which separates the dug-out canoe of a savage from the ironclad or transatlantic liner, and the drawings which primitive man cut on the walls of caves from the epic of the cosmos depicted by Michelangelo on the vault of the Sixtine Chapel. And yet life, that wondrous architect of form and function, has till now revealed but a minimal part of its age-long work of progressive building of organised and living beings. The sum of truth which it can teach to man is still

unlimited and with a progressive mastery of the truths of life man will enhance his dominion over nature, increase the springs of his joy and dry up, as far as is possible, the fount of pain.

The inferiority—a technical inferiority I presume to call it—of conscious will with regard to unconscious functions is probably owing to the fact that will represents the most recent of life's powers. Perchance will still suffers—if I may be permitted so daring an expression—from the inexperience inseparable from its comparative youth; it has not yet excavated by innumerable trials the structures by which it is determined, with mnemonic furrows deep enough to direct its course securely, to be able without hesitation and with minimal effort to bring about effects which will be useful to the individual and the species.

But the superiority of man over all other animals is not only due to his morphological and more particularly to his psychological characteristics; he also enjoys a privileged position thanks to his energetical capacity. The researches of v. Rübner⁴¹ may be remembered in this connection. They could not by their nature lead to indisputable conclusions, but in spite of certain important criticisms the results obtained are suggestive. Only the most significant points will be given. As is well known and as will be explained at greater length in what follows, continuous degradation of energy is required to maintain many forms of life; the intensity of the process depends especially on the extent of body surface. But v. Rübner states that higher animals of divers types—the horse, cow, dog, cat, guinea-pig—from the day on which they reach their full development to that of death from old age, use approximately the same number of calories per unit of body-weight. So that the more rapid their consumption of energy the shorter their life. It follows that small animals are less long-lived than large ones, chiefly because they have to produce a larger quantity of heat per unit of body-weight to compensate for that lost by radiation from their relatively larger body

surface. In point of fact, the horse, after complete development, lives about 30 years, the cow 26, the dog 9, the cat 8, the guinea-pig 6. These data suggest that the duration of life in a given organism may be considered, in part at least, as consequent on the velocity of the current of energy which passes through it. Man, with regard to longevity and consummation of energy, occupies a privileged position, because the quantity of energy which he uses during his natural life is four times that used by other animals, in spite of the fact that the velocity of the current of energy depends above all on the extent of body surface. In other words, he only dies after having used four times more energy per unit of body-weight than that made use of by other mammals and lives therefore four times as long as they. If this could be indisputably proved, not only would man have at his disposal more perfect bodily organs, but he would also possess, in the exceptional span of his life, an advantage which would allow him to acquire a larger experience. He could arm himself better than any other animal for individual and collective defence.

If the time taken for the new-born animal to double its weight, or, in other words, if its rate of growth is measured, it is found to be approximately equal for animals of the same species, *i.e.*, 6 days for the rabbit, 8 days for the dog, 9 for the cat, 14 for the pig, 15 for the sheep, 47 for the calf, 60 for the horse. These figures show that the total mass does not depend on the duration of development, but on the relative velocity of growth which is the greater the smaller the animal. Man is an exception to this rule, because although at birth he weighs one quarter less than a new-born lamb, he requires 180 days to double his birth-weight, whereas the same feat is accomplished by the lamb in 25 days.

It may be further presumed that this exceptional slowness of growth in man is a feature of intra-uterine as well as of extra-uterine development, if we consider the duration of pregnancy in relation to the weight of the offspring.

One example will suffice. Gestation in the cow is accomplished in 285–290 days and the new-born calf weighs 35 kilograms; a human foetus is carried to term in 280 days and weighs about 3 kilograms at birth. In the sheep, a gestation period of 144–150 days is enough for the complete development of a lamb weighing 4 kilograms.

It is said that there is one other exception to this rule besides man, *Anubis Pavian*, a small species of the *Cynocephala*, which has a gestation period of 150–200 days and the offspring of which doubles its weight in 120 days. But these figures require confirmation, the more so when one remembers that the gorilla weighs as much as its mother in only eight years—a rather rapid growth, and that small simians have a type of development similar to that of other animals.

The slowness of growth in man would be accounted for by the hypothesis that he uses for histogenesis a much smaller fraction of the energy derived from food than do other animals. In the latter, energy used for building of tissues represent approximately 35 per cent. of the total, in man only 5.2 per cent. To build one kilogram of tissue in the higher vertebrates, an amount of food, in this case maternal milk, capable of liberating 4,808 kilogram calories would suffice; in man, six times as much would have to be provided, *i.e.*, 28,864 kilogram calories. One may therefore conclude, though with considerable reservation, that to build a man is a slower and more costly work than to build any other of the higher animals. And as we have no reason to acknowledge any great difference between the organs of the one and the other, with the exception of the nervous centres and their appendages on which depends the whole superiority of man, we must conclude that much energy and time are necessary to raise these most delicate mechanisms.

Are not the works of embellishment and refining those which cost the most and which require the longest time for their completion?

Investigations on living beings not only provide valuable information on their behaviour with regard to the current of energy that moves the universe, and on the physical, structural, and chemical determinants of their action, giving to us at the same time a light on the struggle for the conquest of nature, but biological researches help also to explain the correlation between the defensive, tangible acts of the organism *in toto*, as a conscious individual endowed with will, and actions of the single organs of which it consists and which, although unconscious, appear to us to be influenced by the same object of protecting the integrity of the individual whole and the species to which it belongs.

The organs then, seem to be dominated by the higher directive influences which co-ordinate their efforts and guide them towards a common end of adaptation and defence. Truly a marvellous example, showing us physiology, not merely as a natural science, but also as a fount of moral instruction worthy of consideration and of imitation.

“ Das Höchste
Suchst du, das Höchste, das Grösste?
Die Pflanze kann es dich lehren;
Was sie willenlos ist, sei du es wollend.”

Schiller says : “ The highest seekest thou, the highest, the greatest? The plant can teach it thee; what it is unconsciously, be thou voluntarily.”

Thus the study of vegetative life may be not only a guide to material conquests, but also a discipline of our ethical behaviour. This should not astonish us if we do not admit any essential difference between the motives which give rise to unconscious acts and those which determine conscious actions. And truly, while confessing our ignorance regarding the ultimate causal relations between biological conditions and psychological phenomena, who could deny the intimate bonds which link them together, who would dare contradict that our thought depends, not only on the

physical, chemical, and structural properties of our brain, but also on those of the whole organism? It is undeniable, in fact, that the highest mental processes and visceral functions are intimately connected, as is shown by the way they influence each other. Occasionally they influence one another alternatively, so that no clear boundary can be fixed between the conscious and unconscious, and the threshold of the sensorium oscillates continually. Often we catch a glimpse in ourselves of the unconscious passing over the line into consciousness; sometimes, on the contrary, the latter becomes plunged in a darkness which the perceptive powers cannot disperse.

These reciprocal relations and oscillations between the conscious and unconscious and the analogy of their tendencies give ground for hope that the study of the conditions governing them may serve to throw light on their mutual significance. This study may furnish new arguments in support of the idea that unconscious functions are the work of a special agent acting in a manner similar to the will, the same perhaps that in the nerve-centres finds physical, chemical, and structural facilities for revealing itself consciously and which raises man to so great a height of sensorial and voluntary power.

CHAPTER V

EXCITABILITY AND AUTOMATISM

LIVING beings may be considered as mechanisms in a state of constant unstable equilibrium. Indeed their most obvious property is their irritability. By this we mean their capacity for answering readily and quickly to external and internal stimuli even when very slight. The response as a rule has a far greater intensity than the stimulus itself and often has for its object the defence of the individual or of the species. The instability of living beings therefore, paradoxically enough, is the fundamental condition of their integrity, for without these ready and efficient reactions they would be easily destroyed. Although all structural elements possess in a greater or less degree and in different forms the power of responding to stimuli, in the organism considered as a complex whole a special receptor apparatus, external and internal, is provided. This may be roused by stimuli arising either from the outside or emanating from body-humours or tissues, and transmits their state of excitation to the reactive or effector mechanisms. In this way living beings continually adapt their internal conditions to their surroundings, and life is revealed.

A glance at the different classes of vertebrates shows that, on the whole, it is not only general irritability which is increased as we ascend the animal scale, but also the power of discrimination; differentiation on the part of the receptors becomes more subtle and more perfect and the effector responses show greater and more varied adaptation. At the same time, psychic power and voluntary acts acquire greater importance and refinement and are capable

of more complex associations and a greater variety of forms. In this way the organism, by assuming more intimate and complex relations with its surroundings, becomes more vulnerable, but at the same time increases the chances of adaptation and therefore of defence.

This greater vulnerability depends on a more acute excitability in the higher species. This is observed, not only in animals as a whole and particularly with regard to their apparatus of relation, but also in isolated organs, and is easy to demonstrate in the heart. The excised heart continues to beat for varying periods depending chiefly, *ceteris paribus*, on the zoological grade of the animal to which it belonged. The heart of a chelonian, e.g., that of *Emys europæa*, may survive fifteen days or more after removal from the body, even if it goes on registering its beats by means of a lever on a smoked, revolving cylinder; one need only prevent it from drying up.⁴² On the other hand, complicated physical, chemical, and mechanical artifices are necessary to maintain the heart of a higher vertebrate in the living condition even for a few hours.

The facts we have mentioned with regard to the different species may be confirmed by a consideration of embryonic or ontogenetic development, as it was borne out by my studies on the embryonic development of cardiac function in the chick. But before explaining the cause of the varying periods of survival of the excised heart in different species or in embryos at different stages of development, I will take the opportunity of expressing my views on the conditions governing excitability in living beings.⁴³

The energetic potential which forms the dynamic foundation of the functional processes of living beings is derived from food, whether introduced directly from the outside or stored in the tissues as reserve material. In order to simplify the problem, we will consider only the case of an animal whose temperature is constant, although our explanation has a general application. In such animals

the energetic potential is the source of activity of the various functions of the organism, whether they are mechanical, chemical, physical, or morphogenetic. The energy set free for these purposes then becomes degraded and is expelled in the form of heat, except when used for mechanical acts involving external work and for assimilative and partly at least for structural processes, where we must suppose an absorption of energy.

All these functions, however, employ but a small fraction of the energetic potential; by far the greater part is degraded directly and dispersed as heat. Heat is the end-result of katabolic processes, like an excretion which serves simply to maintain the internal temperature of the organism, replacing the heat lost by radiation from the surface of the body.

The existence of so much apparent waste of energy leads us to consider whether it is not the result of some special adaptation of the organism, besides that of maintaining constant its internal temperature. This result could be attained with greater economy if the integument did not conduct heat so quickly, for this, by diminishing the dissipation of heat would render less imperative the struggle for the conquest of energetic values. It seemed therefore wise to find out whether the apparently excessive velocity of the current of energy in animals, which is being considered, is not determined by some other functional necessity besides that of maintaining thermostatic conditions.

We have already said that an organism maintains its existence and that of the species mainly owing to its capacity to neutralise promptly and efficaciously external and internal conditions which threaten it and to procure for itself the necessary matter to convert into energy and for reproduction. Hence it may be said that individuals (and therefore the species) subsist in virtue of the peculiar irritability which renders living beings capable of responding to even very slight stimuli with reactions often more vigorous than the releasing agent that has provoked them. And as a matter of fact, responses nearly always follow minimal

stimuli, *e.g.*, light or sound waves, an almost imponderable fragment of a substance, a slight contact, or other similar factors which, I repeat, in spite of their negligible dynamic value, give rise in the organism to considerable kinetic, thermal, electric, chemical and other manifestations.

These immediate and often violent reactions suggest that living beings exist in a state of instability which is not reconcilable with the chemical inertia of the dynamogenic substances stored in them as reserve food-stuffs (chiefly carbohydrates, fats, and proteins). In order that these very stable substances may be able easily and quickly to release in sufficient quantity, when and where needed, the energy required for the functional reactions of living beings, it is probable that a greater or smaller part of them undergoes continuous modifications whereby they are brought to the threshold of decomposition. Under such conditions, the stimulus which eventually supervenes, even if slight, releases the energy necessary for the functional reaction.

Irritability in living beings, then, would be due to a continuous movement of disintegration of part of those compounds which constitute the dynamogenic reserves; they are transformed into unstable materials capable of being broken down rapidly and completely by the slightest impulse. This decomposition on the part of dynamogenous materials, stored in stable form in the tissues as reserve food-stuffs, might take place by internal action, as in auto-catalysis, or external, as in ordinary fermentations. They would be disintegrated chiefly by oxidation; the process would be continuous though its rate would vary, so that the releasing action which eventually falls on them could determine its explosion. This could easily occur, not only by reason of the presumably unstable character of intermediate products, but also because when a stimulus strikes a substance which is in process of dissolution, it can act with increased intensity by acting as an accelerator. Thus a thrust

produces a greater effect when it is applied to a mass which is already in motion and has overcome the retarding action of friction.

If a suitable stimulus reaches these intermediate products when their energetic potential is not completely degraded, their final disintegration is accomplished with great rapidity and furnishes the energy needed for the functional reaction. If no stimulus reaches them, they continue their slow process of disintegration by oxidation degrading into heat.

To make my conception clearer, I will represent it in a concrete form which, however, does not correspond exactly with what we may suppose happens in living beings. It is known that powder with a basis of chlorate of potassium becomes more dangerous the longer it is kept. This is undoubtedly due to the chlorate which in the presence of oxidisable substances gives rise to products of reduction (possibly hypochlorites) which render the mixture more sensitive to shocks or other external disturbances. In favour of this explanation is the fact that the chlorate containing hypochlorites is dangerous because it explodes very easily even with a minimal percussion. These processes happen in presence of water and in fact the dry mixture keeps much better. Undoubtedly the changes which precede and accompany the explosion of black powder are to be interpreted in the same way. In this case, likewise, there is a first stage of formation of nitrites which then give up the rest of their oxygen to form, among others, the gaseous products, carbon dioxide and nitrogen, which are the chief cause of the kinetic phenomena of explosion. Similar reactions may also develop by auto-catalysis provoking the so-called spontaneous explosions, which are nevertheless caused by some external action, albeit an imperceptible one. If instead, no releasing agent intervenes, decomposition may proceed slowly with elimination of heat. The end-products are not explosive and have been obtained without even partial conflagration.

From what has been said above it follows that the flow

of energy in a living being will be greater, and its metabolism more active, the greater its irritability (that is, the better it is adapted for responding to various agents and the more uniformly it is able to maintain itself on the threshold of irritability for minimal stimuli).

Thus seemingly we can explain why higher vertebrates display so considerable a dissipation of energy in the form of heat, why their expenditure of energy is apparently excessive, and why this flow is greater the more lively the reactive capacity of the organism.

It is known, besides, that in higher animals provided with powers of heat regulation sufficient to maintain the internal temperature constant, even when external temperature is very low, that which we may call complex irritability is very nearly uniform notwithstanding changes in the surroundings. On the other hand, in higher vertebrates which have not a sufficient heat-regulating apparatus, and in a greater degree in poikilothermal animals or animals whose temperature varies, which do not possess this power, the temperature of the surroundings and therefore that of the tissues must be high enough to bring about in sufficient measure those analytic processes which we considered as the chemical basis of irritability. When the external temperature is excessively lowered, these animals, deprived of means of defence against it, fall into lethargy, maintaining themselves on a very reduced *régime* of life in consequence of the slowing of the flow of energy and therefore of the considerable depression in their irritability.

According to this hypothesis, the great dispersal of energy in higher vertebrates is not waste but a fundamental function; for on the dispersal of energy would depend the degree of irritability. It would, in fact, be the expression of the continuous transformation of part of the stable reserve food-stuffs into unstable energetic potential. Those materials are then carried to the threshold of rapid decomposition which takes place under the action of external or internal stimuli. To reach this fundamental object, however, the

living organism has to spend energy continuously. In this way it is able promptly to protect the integrity of the individual and of the species. The flow of energy would therefore be the most concrete expression of the effective capacities of a given being for individual and collective defence. It appears, moreover, as a condition necessary to the perfection of the organism, at any rate within the limits of the individual cycle, not only because it refines and elevates the reactive possibilities of the organism, but also because it forces it to work and struggle continuously and vigorously for the conquest of the food values necessary to maintain the very rapid flow of energy which traverses and activates it.

And now, after this brief digression on the chemical substratum of excitability, let us return to our examination of the relations between it and automatism.

As I pointed out at the beginning of this chapter, a tissue or an organ separated from the organism and not put into artificial surroundings survives longer when it belongs to lower vertebrates, than in those having a higher structure. Thus, to limit ourselves to the heart, it is seen that in fishes, batrachians and reptiles the organ continues to beat for a long time after excision, while in birds and mammals its beating ceases very soon.

The experiments on the length of time that the heart survives in fully developed animals were repeated by me on embryonic hearts in different stages of development, in order to find out if what was observed regarding the resistance of isolated hearts in different animals with reference to their position in the zoological scale would be paralleled by the modifications which that organ undergoes during ontogenetic development.⁴⁴ For this purpose I incubated, naturally or artificially, numerous fertilised hen's eggs which I opened at different periods to obtain embryos at different stages.

The embryo having been isolated, it was transferred to a large glass slide, either keeping intact the relations between

embryo and heart, or excising the latter organ as far as possible without injury to its walls, and examined microscopically under a low power. The developing heart was kept under continuous microscopical observation, in order to determine as precisely as possible the duration of its rhythmic activity, which naturally diminishes in frequency and amplitude until its complete arrest. It was seen at once that isolated hearts survived for a shorter time than those left in connection with the embryo, but the difference was not great, probably because the isolation of the embryo already involved serious trauma. In both cases the preparation was immersed in a physiological solution maintained at a constant temperature of 38° C. by means of a warm stage. I should add that these experiments were performed mainly on isolated hearts. I will refer only to results obtained under these conditions because I hold them to be of greater significance.

Experiments were performed on embryonic hearts at varying ages from 3 to 12 days. I have not experimented on hearts in a later stage of development, because the period of survival is then very short. A graphic representation of the data collected on the survival of hearts in gradually increasing stages of development shows a curve descending rapidly from the third to the fifth day, rising then slowly to the ninth day and falling again rapidly to the twelfth day.

This is not the place in which to refer to the numerical values collected in these investigations. I will only say that they showed that the time of survival in hearts at different stages of embryonic life diminishes as the organ develops, parallel to what is observed in comparing isolated hearts of animals representing ascending degrees in the zoological scale. Thus while the heart of an embryo chick of the third day may continue to beat more than an hour and a half after isolation, that of a chick at term survives scarcely three minutes after removal.

The longer survival between the fifth and the ninth day

of development may find its counterpart in the greater resistance of the isolated heart in tortoises compared with that of batrachians. But the probable explanation is that the larger size of the more advanced embryos allows the heart more easily to withstand removal. That, in later stages, the time of survival of the heart diminishes notwithstanding the increased volume of the embryo, may be attributed, as we shall see, to the development of new functional conditions. If we reflect on the conditions which might seriously weaken the heart's vital capacity, we can already *a priori* suppose that the more developed an organ the greater must be its capacity to feel the action of external agencies. Their influence, therefore, will be all the more injurious in the highly abnormal conditions which follow the operation of removal and the numerous and varied changes of which it is cause. In other words, the lessened resistance to isolation of the more developed heart is due to its greater excitability. I do not see how these facts could be otherwise interpreted. Experiment has, as nearly as may be, confirmed this hypothesis, because a faradic current too strong to be borne on the tip of the tongue hardly modifies the rhythm of the heart in the first stages of development, even when applied for a long time. The heart also shows itself refractory to mechanical stimuli, as its resistance to the grave trauma attending excision would be enough to show. I should state that in these investigations I used technical means which allowed me to note even slight modifications in the frequency of the rhythm; moreover, with regard to the amplitude of the contractions, I could not discover any notable variation in hearts in the first stages of development, though I used stimuli shown to be effective with more developed hearts.

From these and similar experiments it may be concluded that the heart in an early embryonic stage may function vigorously, although its excitability, towards electrical and mechanical stimuli at any rate, appears very low, especially

when compared with that observed in other contractile organs and in the heart of adult animals. But this excitability increases rapidly; from the third to the twelfth day of incubation it is more than trebled. Besides plotting the curve of the time of survival, I wished to record graphically the approximate intensity of faradic stimuli capable of modifying the heart frequency in the various stages of development. I marked them with an opposite sign in order to show that the sudden changes in the threshold of excitability vary inversely with the minimal effective stimulus. In this way a tracing is obtained which intersects that of

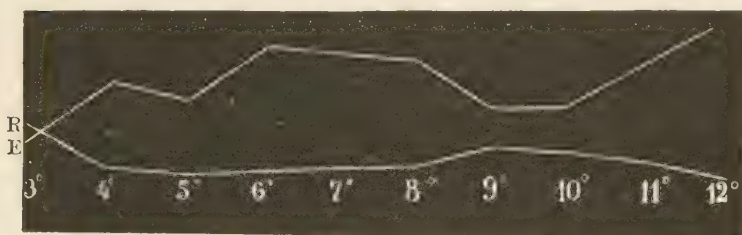


FIG. 13.—The line R indicates rhythmic activity from the third to the twelfth days of development, and E the respective degree of excitability at the same embryonic stages.

the time of survival. It shows that the progressive diminution in the time of survival in the isolated heart is accompanied by a corresponding increase in its excitability. This relation is further shown in secondary details, because the transitory increase in resistance observed from the fifth to the ninth day finds its counterpart in the diminution of excitability seen during the same period (see Fig. 13).

These results do not need special comment, because it will be readily understood, as pointed out above, that the more unstable an organ the more excitable it is and the more it responds to the influence of modifications in its surroundings, and how, in conditions of increased excitability, the stimuli which reach it can penetrate into its structure to alter more or less profoundly the determinants of its function.

And here I find it convenient to recall a few old observations from the great treatise of Milne-Edwards—a mine of information too often forgotten in our days.⁴⁴

Templer, having opened two hedgehogs during hibernation and dissected out the heart, saw the organ perform alternate movements of systole and diastole for 2 hours.⁴⁵

Mangili in his experiments on the comparative duration of muscular irritability while in the active and hibernating phases,⁴⁶ found that the heart continued to beat for more than 3 hours after decapitation in hibernating marmots, while in other animals of the same species taken two months after their winter sleep, cardiac movement ceased entirely in less than 50 minutes after operation.

Marshall Hall⁴⁷ obtained still more remarkable results in analogous researches made on hedgehogs. Section of the medulla oblongata in an awakened animal caused cessation of contractions in the left ventricle and after a few minutes in the auricle also, whereas the contractions of the right ventricle ceased after about 2 hours. But in a dormant animal the same physiologist, after having cut through the medulla, saw the heart movements continue regularly and vigorously for more than 10 hours. Contractions only ceased 11 hours after the operation. No one doubts that in a hibernating animal excitability becomes profoundly lowered in all its manifestations; and it is precisely under these conditions that the heart longest resists changes in the surroundings which, in a heart whose excitability is normal, would produce rapid cessation of function.

These clear examples of the antagonism between the degree of excitability and the time of survival of the function in the heart bring fresh support to the theory which derives the fundamental conditions of cardiac rhythm from the automaticity of the apparatus determining them.

Cardiac excitability not only increases gradually during embryonic development, but it persists longer than the

power of spontaneous contraction. If the threshold of excitability is estimated in an embryonic heart in the later stages of development, after the automatic rhythm has ceased, it will respond with a series of contractions to a stimulus which was incapable of modifying spontaneous pulsations in a less developed heart. Here is an example :

An embryonic heart of 8 days ceased to beat spontaneously 30 minutes after excision (the observation was carried out with the technique described above). Its excitability to faradism was 18, *i.e.*, notably greater than that of a heart of the third day which, while beating spontaneously, presents an excitability of scarcely 6.5.

As for all tissues, increase of temperature within certain limits increases excitability in the embryonic heart. Thus in an excised heart of 12 days, excitability was 23 at 38° C., while at 16° C. it was only 16.

Also the spontaneous rhythmic function responds in similar manner to alterations in temperature. An excised heart of 3 days' development kept at 38° C. beats with great frequency and perfect regularity. After 10 minutes' observation, the temperature is lowered to 16° C. One minute later it begins to slow down and in a short time the beats cease altogether. When the temperature is raised again to 38° C., it suddenly begins to contract and soon regains the rhythm which it had before the cooling. This does not, however, necessarily prove the dependence of function on excitability; it is possible that a certain temperature is necessary for the metabolic conditions on which depend the rhythmic phenomena of the embryonic heart.

That the rhythmic function is independent of excitability may be shown in other ways. The heart of a 3 days' embryo is kept at a temperature of 40° C. After 80 minutes it ceases to beat spontaneously but responds with groups of contractions every time it is excited with adequate stimuli. If it is then removed from the warm chamber and exposed to room temperature of 14° C., it begins to

beat with a slow but perfectly regular rhythm. If it is stimulated by a faradic current, its frequency is increased only when the stimulus is considerably greater than that which is efficacious at a higher temperature.

In this last experiment I diminished excitability by means of cold and brought about a return of the contractions. Thus I obtained proof of the converse of what was observed in embryonic development when increase of excitability shortened the time of survival in the excised heart. By means of these latter investigations which gave results analogous to those obtained by Marshall Hall on the heart of hibernating hedgehogs, it was shown how stimuli which act on a relatively excitable embryonic heart may arrest its function either because they destroy the conditions determining rhythm—and this may happen when irritability is excessive—or simply because they slow or stop it. An example of this temporary arrest we could have, cooling the embryo heart, thus diminishing irritability and allowing resumption of the function which an excess of excitability had arrested. Of course this would not have been possible if the factors releasing the rhythm thus slowed or checked had been destroyed. Therefore it is yet more obvious that rhythmic function in the heart does not depend on excitability, for excitability itself may be a cause of its temporary or complete arrest.

To the arguments put forward up to now in support of the automatic nature of the cardiac rhythm in the embryonic period I can add others which follow from the behaviour of that function during survival.

In fact the embryonic heart, after having contracted regularly for a certain time, presents various arrhythmias. Often they appear as periodic positive or negative groups, *i.e.*, either formed by series of frequent pulsations intercalated in a regular, but very much slower rhythm, or by groups of beats separated by pauses of varying duration; and this happens while the external conditions remain unchanged. The discussion of these facts would lead me too

far. I will only recall *à propos* of the periodic respiration shown by *Emys europæa*⁴⁸ during hibernation, and the perambulation, eventually periodic, seen in the same animal after decerebration, that I have tried to demonstrate how the transformation of rhythmic into periodic movements is the result of conditions lowering the automatic capacity of the nerve-centres from which they emanate. So that the periodic functional phenomena in organs which are near exhaustion and which normally work rhythmically is an important argument in favour of their automatic nature.

A casual observation furnished me with another contribution in favour of this automatic theory. A chick embryo early on the third day, when isolated and placed under the microscope in the normal conditions of humidity and temperature, was found to have a double heart. In this embryo the two cardiac tubes, perfectly distinct one from the other, were touching at their convexity and presented the form and relations described by Dareste in his "Tératogénie expérimentale."⁴⁹

Apparently the conditions under which these two hearts existed were identical. They were in the same stage of development, of the same shape and dimensions, of the same minute structure, and had similar relations in the same organism; they contained the same fluid, were immersed in the same solution, maintained at the same temperature, and in such close proximity that the most hypercritical mind could not have detected the slightest difference in the conditions in which the two hearts were placed. Nevertheless, they did not beat in the same way. The heart on the right side from the very beginning of the experiment showed a rhythm less frequent than that on the left side; later, when a negative periodic rhythm appeared in the right one (*i.e.*, groups of contractions occurring at intervals) the heart on the left continued to beat perfectly regularly. But, admitting the identity of the conditions surrounding the two hearts and allowing that there was no difference between them in form, dimensions and

intimate structure, and that the stage of development was certainly the same, if, nevertheless, they behaved so differently, we must agree that their identity was only apparent and that there were differences between them which eluded direct observation. After what has been said with regard to the conditions of their preparation and examination, the only difference one could imagine was a variation, quantitative if not qualitative, in their metabolism. *À propos* of this, we may recall that Dareste states that the heart is normally double in its first stages, and he attributes the direction of the curvature in the embryonic organ to an accession of growth on the part of the left cardiac blastema. Accepting Dareste's theory, one may suppose that the more intense assimilative power of the left heart would be the condition determining its greater functional activity.

From what we have said, it follows that in the embryonic heart the respective values of functional activity and excitability do not present a parallel course and that at times they are even sharply divergent. So that the organ might have a rhythm ample, frequent and lasting, without the possibility of any stimuli in the surroundings which could be considered as the freeing agents of its function. At the same time the high threshold for excitability of the organ would exclude, at any rate in the earlier stages of development, efficacious action by outside stimuli.

It is known besides that in this first period the embryonic heart is composed of cells which are so much differentiated as to resemble those of contractile tissues; nor can nervous elements be traced in it as yet. Nevertheless, as we shall see later, its function evolves with perfect rhythm and in a peristaltic form identical with that of the adult heart. Although I have always been a partisan of the myogenic theory of cardiac rhythm, I will not insist on the significance of a perfect function developing in the absence of nervous action, because a similar argument in favour of the myogenic origin of the heart beat, if applied to the developed heart

rich in nervous elements, would present a target for obvious objections. But one thing is certain : since the embryonic heart beats regularly even after excision and is refractory to strong stimuli, the rhythmic function must be a condition of its intimate functional structure and not derived from its surroundings. The determining cause must be sought in the metabolic activities carried on in the structural elements of the organ. In other words, the rhythmic pulsations are truly the consequence of automatic impulses similar to those described in the previous chapter in speaking of the ambulatory node of the bulb. They are phenomena which may be modified, inhibited, or definitely arrested by external stimuli, but they owe their rhythmic character to intrinsic conditions of the contractile elements which perform them. With its later development, the heart undoubtedly acquires the power of reacting to external stimuli and becomes provided with an intrinsic and extrinsic innervation which renders it better able to adapt the amplitude and frequency of its contractions to the immediate requirements of the circulation. But the factors releasing its rhythm remain essentially automatic.

I demonstrated a similar phenomenon in the respiratory centre of *Emys europæa*. Both these rhythmic functions, on which the life of the organism depends, must be carried on unceasingly, because death follows inexorably on their arrest. They are bound up with organs which are fundamentally automatic and which carry the conditions for the maintenance of their activity in the intrinsic chemical changes of their cells and not in external stimuli. Thus continuity in their rhythm is better assured than if it depended on the changeable conditions of the surroundings. External conditions, however, act directly or indirectly on the factors of the function, adapting it to the various situations which the organism has to meet in the multiform activities of its life.

The antagonism between excitability and automatism is brought out, not only by the experiments just described

on the embryonic heart, but also by those on the ambulatory node of the medulla which formed the subject of a previous chapter. They show that direct influence of excitability on the movements of the bulbo-spinal animal may be excluded; on the contrary it may be affirmed that external stimuli in general have rather a moderating effect on the movements of perambulation of the decerebrate tortoise. The above-mentioned antagonism was shown even more clearly by experiments, some old,²⁶ and some other recent,²⁸ performed in collaboration with Dr. G. Zampa. In the first place we must remember that it is only in highly resistant animals that we can observe automatic perambulation after extirpation of the optic lobes. If, for example, this operation is performed on frogs and toads, the movements described above appear constantly in toads, but in the frog they have never been seen in spite of repeated attempts. Besides, neither asphyxia following obstruction of the trachea nor anæmia of the medulla produced by an elastic ligature round the neck has brought about changes in the behaviour of our bulbo-spinal tortoise, unless, by prolonging these conditions, bulbar metabolism has been profoundly disturbed.

All this confirms the belief that perambulation in decerebrate animals is not due to extrinsic stimuli, humoral, nervous or external, but to conditions intrinsic to the centres from which emanate the impulses for those movements.

Other investigations lead to the same conclusions.

To the tail of a bulbo-spinal tortoise is tied a small brush dipped in a solution of an aniline dye and connected with a pipette filled with the same stain, in such a way as to trace on the floor of the laboratory the outline and distance covered by the animal. By this means I ascertained that an animal which showed periodic perambulation at long intervals progressed at an average rate of 10·25 metres an hour. I then injected subcutaneously 0·5 c.c. of a 1 in 1000 solution of strychnine sulphate. On the follow-

ing day, as was to be expected, the animal became extremely excitable; it responded with powerful reflex movements to taps on the floor or on its shell, but without ever showing tetanic spasms. Left to itself, it walked very slowly, by short groups of ambulatory movements alternating with long pauses; the average speed was scarcely 1.30 metres an hour. The next day I made another injection of strychnine. Although the tortoise showed great reflex excitability for several days, it did not move again. This experiment was recently repeated and gave the same results.

Let me record another experiment :

A bulbo-spinal tortoise showed the usual perambulation, which, however, was rapidly becoming less. The experiment was made in July and the room temperature was 27° C. Exhaustion often occurs in summer and it seems fair to attribute it to the high degree of excitability shown by the animals in this season. This hypothesis was confirmed because after injection of 10 centigrams of ammonium bromide, the tortoise was seen to move with greater vigour. The same observation was made in another bulbo-spinal animal after the injection of 2 mg. of morphine hydrochloride.

But although the fundamental cause of perambulation is automatic and is localised in the bulb, one cannot deny the influence of internal or external stimuli. And, indeed, all the experiments described above on the depressive action of excitability on automatism lead to this conclusion. To which may be added what we know relative to the action of respiratory and cardiac innervation on the automatic phenomena of the respiratory centre and the heart. We have likewise seen how the central mechanism of voluntary acts appeared related to inhibitory influences on the ambulatory centre. The latter in their turn are obviously set in action by the external and internal stimuli which lead to the release of the volitive act. These relations between excitability and automatism are made yet

clearer by some experiments showing not the negative phenomenon of arrest, but the positive one of movement. They were performed on three tortoises and gave the same results in each. The fore-brain, intermediate brain, and a great part of the mid-brain were removed, leaving behind only a narrow strip of the posterior part of the mesencephalon. These animals never moved spontaneously, but behaved like lobo-bulbo-spinal animals, as if the small portion of the optic lobes left intact was sufficient to inhibit completely the automatic activity of the ambulatory node. But if the shell of the tortoise was touched even lightly, or if the tail was pinched, they at once performed a series of excessive ambulatory movements characteristic of bulbar animals. The groups of movements thus incited were always about of the same duration; hence the distance passed by the animal was nearly always the same. For instance, one of the three animals, after any stimulus, covered a distance of about one metre.

These tortoises obviously represent an intermediate stage between bulbo-spinal and lobo-bulbo-spinal animals. They have not the spontaneous perambulation of the first, nor the tonic, active inhibition of the second. The ambulatory bulbar movements are certainly arrested, but one is dealing with a weak inhibition, easily overcome by external stimuli. These act either by checking inhibition, or by intensifying the conditions determining automatic activity in the bulb, thus neutralising the feeble inhibitory action exercised by the fraction of the optic lobes left *in situ*.

Let me now summarise the conclusions already set forth in this necessarily incomplete exposition.

Certain essential functions, the cessation of which would mean death, *e.g.*, that of the heart and of the respiratory mechanism, are fundamentally automatic; their rhythm is not due to internal or external stimuli acting either directly or through the nervous system, but to a nutritive cycle in the cells which perform the movement. These functions are preponderatingly automatic in lower zoo-

logical types and in the earlier stages of embryonic development in higher animals, but, with the rise of the organism in the zoological as well as in the ontogenetic scale, the apparatus for releasing mechanical stimuli becomes progressively more excitable and more capable of responding intensely and adequately to casual stimuli. The uniform automatic function is thus adapted to the requirements of the whole being. The organism, just because it becomes more complex, more excitable, and therefore more unstable, requires a more adaptable respiratory and circulatory apparatus, that will harmonise promptly with its various and pressing needs.

CHAPTER VI

ON THE RELATIONS BETWEEN EXCITABILITY AND AUTOMATISM DETERMINING CARDIAC PERISTALSIS

IN the preceding chapter I began an account of my investigations on the embryonic heart in the first stages of development; an attempt was made to establish the cause of its remarkable resistance to injury and the fundamental property which determines rhythm in an organ not yet differentiated into muscular and nervous tissues. These investigations led me to the conclusion that its resistance depends on very low excitability and the rhythm on a peculiar automatism of its walls.

I should add that the latter, notwithstanding their primitive structure, develop rhythmic contractions which, like those of the adult heart, are propagated as peristaltic waves from the venous to the arterial extremity. I was interested in finding out those intrinsic conditions of its wall to which this process should be attributed.⁵⁰ For this end I used special methods which I will describe in detail so that the difficulties which had to be overcome may be understood. But had the technical complications been even greater, I would still have attempted the problem; for the minute organ scarcely visible to the naked eye, which from the third day of incubation reveals the alternations of its function, reddening when it expands and turning pale when it contracts, is, in the immobile and deformed rudiment of the embryo, the first tangible symbol of life. It is a beacon calling the investigator to penetrate the mysteries of existence. Ever since my student days, the

embryonic heart has been the goal of my researches. I used to keep a home-made incubator in my room, in order to give myself the thrill of contemplating with microscope or naked eye the first palpitations of life.

What hidden marvels lie concealed in the walls so thin, transparent, and seemingly uniform, of that *primum movens* destined to work unceasingly from the first beginnings to the final close of life ! It is a theme for the poet as for the physiologist. And should not the physiologist feel all the poetry which emanates from the vibrant woof of living tissue, in order to enable him by intuitive vigilance, combined with rigorous and appropriate technique, to illuminate some aspect of the numerous and complicated problems which it presents for his investigation ? Should he not be infused with "intelletto d'amore" ? But all too often the sage lacks love; and those that love lack wisdom. As Shelley laments in his "Prometheus Unbound"—

"The wise want love; and those who love want wisdom."

But let us fold the wings of sentimental boldness and attend to the humbler task of describing the methods employed to investigate the conditions determining the type of contraction in the embryonic heart of the third day of development.

Everyone knows how the centre of gravity of the yolk of the hen's egg (I confine myself to it) is situated in such a way that the embryo always finds itself on the upper side* this is obviously in order that it may feel the direct influence of the heat of the hen's body which is above it. This arrangement is very convenient for the experimenter who is certain of uncovering the embryo as soon as he has

* An analogous arrangement was found by D. Rosa [*Sull' orientamento dei primi stadii nei cordati*. Atti d. R. Accad. d. Scienze di Torino. Vol. LX., 1925] in the eggs of the inferior chordata, which gives to the embryo a convenient position. It appears as though this adaptation had been later applied in the birds to the exigencies of incubation. (Author's note.)

removed the calcareous and membranous involucra, provided he breaks through at a point above the equatorial line of the egg.

After 3 days' incubation, the egg is opened, keeping it immersed in a physiological solution at 38° C.; the embryo is removed by a circular incision and placed on a slide. The amniotic sac is then opened and the heart is thus exposed and isolated by further dissection.



FIG. 14. —Embryonic heart at third day of development, isolated and fixed by means of platinum wires, X Y.

O = auricular end.

V = ventricular end.

AB, CD, EF, GH indicate the lines of section of the heart that were practised, as explained in the text.

When it is required to fix the heart as well as to isolate it, two tags of embryonic tissue are left at its upper and lower ends. The tags are then fastened by two platinum wires placed transversely at a suitable distance on the bottom of the moist chamber. This arrangement is shown in Fig. 14; O and V indicate the dorsal aspect of the tissue adjoining respectively the venous and arterial extremities of the heart; the platinum wires, X and Y, fixed to the wall of the moist chamber are placed on the fragments of embryonic tissue which are in relation respectively with the auricular and ventricular portions of the heart. The moist chamber is then filled with physiological solution, is introduced in a thermostat regulated at 38° C. and

the whole is placed under a low-power microscope.

Some of these investigations were made on hearts maintained in connection with the rest of the embryo, others on isolated hearts. I wished, moreover, to discover whether the different regions of the embryonic cardiac tube could be distinguished functionally one from the other. In order to do this, I divided the heart into different portions, making the sections at given points by means of the apparatus shown in Fig. 15. It consists of a glass slide

on which are fixed two small metal blocks each of which is divided by a groove containing a small, very sharp blade furnished with a handle. The latter can be lowered so that its edge comes in contact with a very fine line drawn on the slide. It will be understood how with this small apparatus it is possible to section the embryonic heart in any way required. The heart is moved on the slide so that the section to be made corresponds to the line engraved on the glass and the guillotine is then lowered by pressure on the

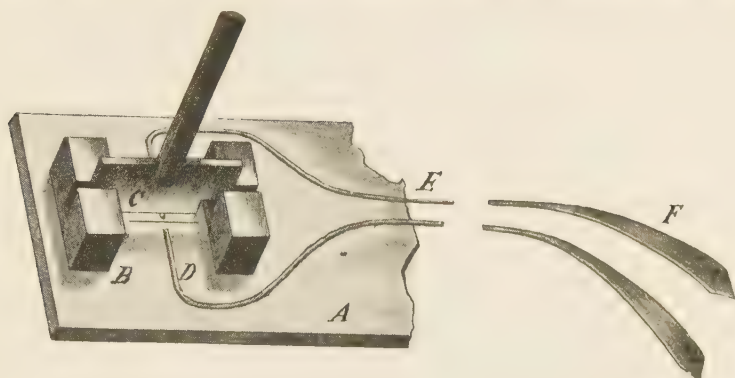


FIG. 15.—Section apparatus for the embryonic heart.

A = glass slide.

C = blade working in grooves in two metal blocks, one of which is indicated by the letter B.

D, E, F = platinum wires which can be connected with a faradic coil and which end at the sides of a fine line engraved in the glass slide.

handle. By this method I was able to section the embryonic heart of the third day and even that of the end of the second day, in minute transverse and longitudinal portions. On the same slide as the guillotine apparatus, facing each other on each side of the engraved line, are fixed two platinum wires connected with the secondary circuit of a faradic sliding coil which serves to measure approximately the degree of excitability of the different regions or the separate fragments of the heart.

I also wished to record graphically the function of the embryonic heart in order to have documentary evidence of

the facts observed, and above all to measure certain functional relations and investigate details of the form and direction of the cardiac cycle which cannot be made out by simple inspection. For this purpose, given the small size of the heart and its dynamic power, the photographic method is the only one possible; for it allows the use of

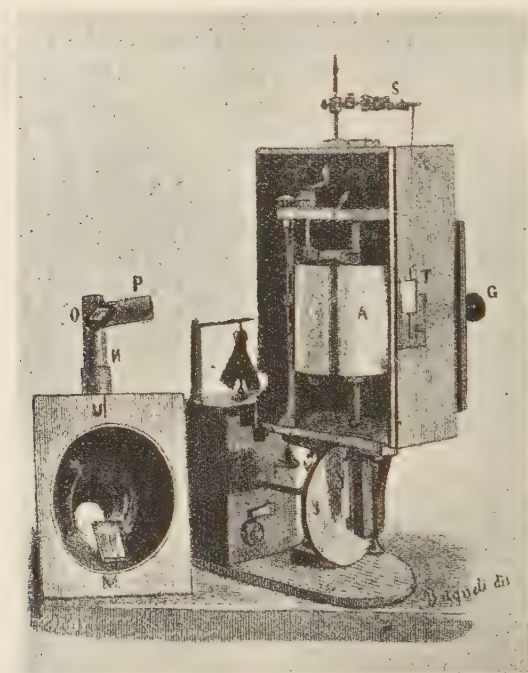


FIG. 16.

For legend see FIG. 17.

an imponderable lever whose excursions can be enormously magnified and which does not need to be attached to the organ under examination, a lever in fact, made of luminous rays. These investigations, carried out more than 30 years ago, are, I believe, the first attempt at photographic records of movements of an almost microscopic organ.

The image of the beating heart is projected on to a highly sensitive film revolving around the cylinder (see Figs. 16

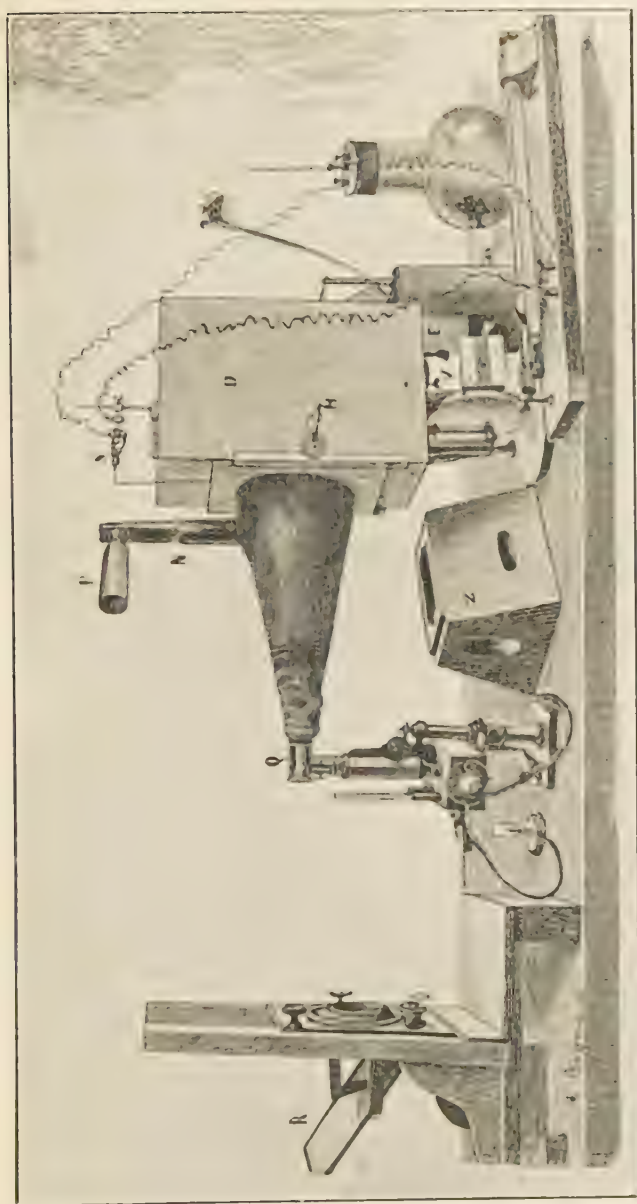


FIG. 17.

FIGS. 16 and 17.—Apparatus for photographically recording the rhythm of the embryonic heart at the third day.

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and 17) of an ordinary drum. The cylinder is enclosed in a rectangular box divided into two parts adapted perfectly to each other and fixed by means of clasps so as to keep the cylinder in complete darkness and yet allow of all the manipulations necessary to charge the apparatus, to modify the speed of the cylinder, and to stop, start, raise, or lower it. On the front wall of the box is a slit which can be opened or closed by means of a screw to alter its width as required. In the same wall, in two lateral grooves, runs a wooden slide with an elliptic opening which is surrounded by the base of a cone, as in many projection apparatus. Inside this, on its lower part, is fixed a plane mirror inclined in such a way as to reflect the image of the slit above it and vertically, and on its upper part is a tube bent to a right-angle, with a small plane mirror fixed at the angle between its horizontal and vertical portion and inclined 45° so as to reflect the image from the larger mirror along the horizontal arm of the tube. The cardboard cone is joined by means of opaque black material to a horizontal tube carrying a redresser prism which projects the magnified image of the heart horizontally.

When I carried out these investigations it was 30 years ago and I had no electric light in my laboratory. I was therefore obliged to use sunlight. This was often a sore trial to my patience, because it would happen that on the day fixed for the experiment, when the egg had reached the required maturity, the sky was overcast, or at the most important moment an unwelcome cloud would cover the source of light.

From the description of the apparatus it is easy to make out how it works. The image of the heart, magnified by the microscope, is projected on the sensitised film wound round the cylinder. The experimenter, looking in the horizontal tube, P, sees at the same time the sensitised film through the slit and the image of the embryonic heart. He can then focus the latter exactly on to it and establish relations between the image of the heart and the slit, and

even watch the progress of the experiment while remaining in full daylight.

As has been said, I was chiefly concerned with the embryonic heart in the period of development from the end of the second to the third day, *i.e.*, from 46—68 hours of

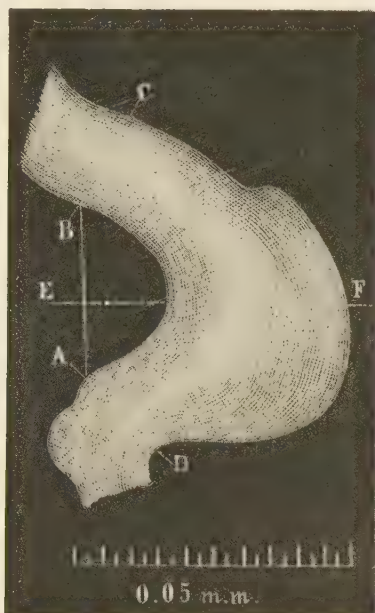


FIG. 18.—Image of the embryonic heart at the third day of development seen as enlarged in these observations.

Every division in the scale corresponds to 0.05 mm., and the whole scale to 1 mm. A B = line corresponding to the slit in the recording apparatus. A D = venous or auricular extremity. B C = arterial or ventricular extremity. E F = conventional line dividing the arterial from the venous region of the heart.

incubation. But my records are mainly of the last stage, for the heart of the second day is too transparent to give a satisfactory photographic impression. The heart on the third day, when excised and slightly drawn out at its extremities so as to overcome its natural form of a spiral, is shaped like a stomach; this is shown in Fig. 18. At the venous extremity, A D, two slight bulges can already

be seen, which when developed will form the auricles; next to them is an important expansion, EF, the fore-runner of the ventricles; then follows an attenuated tube which corresponds to the bulbus arteriosus, BC; a slight constriction separates the auricular from the ventricular region and there is another, less marked, between the ventricle and the bulbus. For the sake of brevity we will speak of the venous or auricular and of the arterial or ventricular extremities, meaning thereby the points AD and BC respectively in Fig. 18 in the intact heart. By the expressions auricular or venous and ventricular or arterial, I mean, on the other hand, the parts which, in the divided heart, remain in relation with the corresponding extremity. The concave border, which is, of course, the shorter, measures on an average 1.80 mm. while the convex is 2.56 mm. In the tracings registering at the same time the auricular and the ventricular beat, in the intact heart it is only the parts BC and AD of Fig. 18 which appears on the graphic record, because the slit represented in Fig. 18 by the dotted line AB runs between them. This part of the concave border AB is 0.92 mm. in length, whereas the corresponding convexity CD measures 2.18 mm.

The heart is arranged in different ways for the experiment, according to the kind of tracing desired. When it is simply a question of recording the contractions from the time of excision till death, the tissue connected with the extremities of the heart is fixed under the platinum wires as already described and the image of the heart projected in such a way that its broadest and most opaque portion, corresponding to the ventricle, falls on the slit of the registering apparatus. Thus with systole and diastole of the heart, the illuminated portion of the slit lengthens and shortens, and a negative tracing corresponding to the complex rhythm of the embryonic heart is registered on the film (see Fig. 19). In order to obtain a simultaneous tracing of the auricular and the ventricular region separated from each other by means of the guillotine apparatus, each part

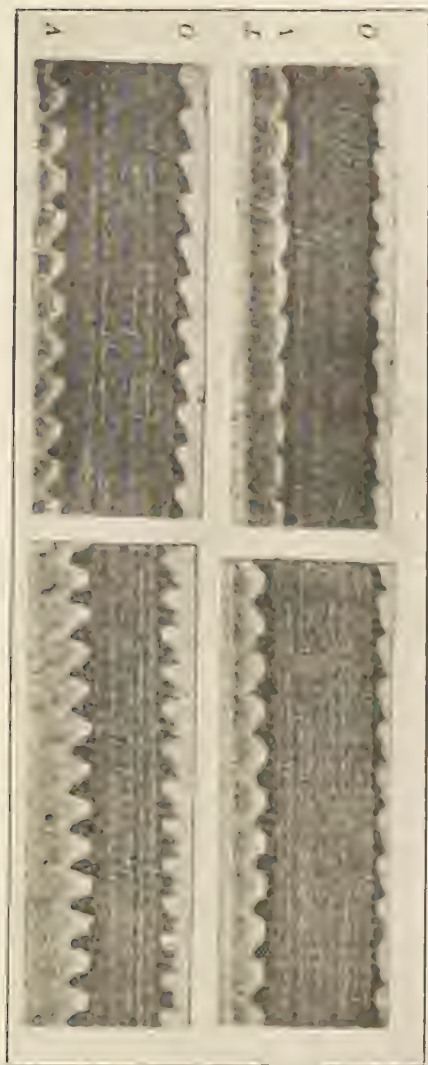


FIG. 18.—Photomicrographs of the auricular and ventricular rhythm of a heart at the third day of development. They run from left to right.

V = ventricle. O = auricle. T = time, in tenths of a second.
The outlines, in the originals, are much sharper than in this reproduction.

is fixed to one of the platinum wires in the moist chamber and their image is projected so that they cover respectively the upper and lower ends of the slit. Thus each part of the heart shortens and lengthens the slit and registers its contractions on the same ordinate.

Finally, if the contractions of the auricular and ventricular extremities are to be registered separately in an intact excised heart, the two ends are fixed to the platinum wires as already described, but so that the heart is doubled up into a U shape and the image is then projected in such a way that the auricular region occupies the upper end of the slit and the bulbar its lower end, as is schematically outlined in Fig. 14 and better shown in Fig. 18. With this last arrangement I have been able to record on the same ordinate and separately the movements of the auricular extremity and of the ventricle of the intact embryonic heart, and at the same time have succeeded in measuring the speed of transmission of the peristaltic wave of contraction from the venous to the arterial extremity. With the photographic method just described I have also been able to obtain tracings recording the action of gas on the isolated embryonic heart. But I will only describe the results strictly relevant to the conditions determining the form of the peristaltic wave of the heart beat.

An embryonic heart, recently excised, shows frequent and ample contractions which invade the whole auricular region almost instantaneously. The contractions are then transmitted to the ventricle, but with a slight retardation, which is less obvious the more frequent the beat. The ventricle then contracts but less rapidly, because in it the progress of the peristaltic wave is markedly slower.

The embryonic heart after being separated from the organism usually continues to beat for rather more than an hour and it may happen, although exceptionally, that it survives for three hours and a half. On this question I join issue with Preyer and Wernicke, for although an excised heart must be considered to be near death, this does not

prevent it from beating with a perfect rhythm for a fairly long period, sometimes more than two hours. But after this first stage, it shows symptoms of exhaustion which, while revealing themselves in different ways, occur constantly. The heart beats gradually become less frequent, although at first a regular rhythm is maintained; this then passes over into a periodic phase consisting of groups of regular contractions alternating with pauses; finally there is an irregular succession of contractions similar to those which Luciani in his work on the frog's heart called crises. As in the adult heart, so also in the embryo, the ventricular part has less resistance than the auricular. Indeed, the ventricle, which at first keeps pace with the auricle, after a certain time begins to beat less frequently and assumes a periodic rhythm when the auricle is still contracting normally. In the last stage ventricular crises occur while the auricle may have a periodic or even a regular rhythm. It is therefore evident that even in the first stages of embryonic development the ventricle shows less resistance to the injury attending excision than the auricle.

Besides the usual periodic rhythm consisting of groups of beats separated by a pause which we may call negative periodicity, I have observed and recorded a periodicity that I call positive. Groups of very rapid beats interrupt the slow rhythm of a heart near exhaustion. Sometimes these forms of periodicity succeed each other, at other times one of them appears during a long course of regular beats. In other cases, the periodicity may take on a special form, which we may call intercurrent periodicity; that is, the contractions pass suddenly from a regular rhythm to periodicity, then become regular again and so on, showing, in fact, a regular course intercalated with periodical forms.

I take the opportunity to repeat in this connection that the phenomena I have described were observed on hearts kept as far as possible under constant extreme conditions and therefore the cause of the variation in their function must be sought, chiefly, at any rate, in the wall of the heart

itself and not in the surrounding medium. The normal rhythm, the positive, negative, or intercurrent periodicity, the crises, the greater liability to exhaustion of the ventricle, compared with the auricle, are, in other words, not merely the expression of a variation in the relations between external stimuli and cardiac excitability, but rather the result of intrinsic changes in the nutritive cycle of the heart-wall. These changes depend on the quantity of dynamogenic material available and on the possibility of renewing it and using it for movement, independently of external stimuli. External stimuli may certainly bring on more or less rapidly and profoundly the signs of cardiac exhaustion, but obviously they do not determine the form, of course, of the heart's function. Protected by its lack of excitability, the heart, by its beating, gives a tangible expression of its integrative and disassimilative activities.

After having studied the form, duration, and range of the action of the isolated heart, I investigated the conditions determining the course of its peristaltic movement. This is seen as a wave of contraction beginning always in the venous region and spreading to the arterial extremity. It is remarkable that the embryonic heart during the first days of development, when cut into minute pieces, shows rhythmic contractions in each of them, so that at first sight one might conclude that the automatic function is equally distributed in all its cells. It might also be supposed that the severe injury attending the sectioning acts as a continuous stimulus, determining rhythmic contractions in each piece of the heart,⁵¹ for the embryonic like the adult heart responds rhythmically to a continuous stimulus. But in order to accept this explanation, the very low irritability of the embryonic heart in the first stages of development would have to be discounted. I therefore resumed these researches by sectioning the heart in different ways by means of the guillotine apparatus described above. It was also possible merely to produce a linear bruise which injured the tissue without bringing

about solution of continuity between the auricular and ventricular regions. This was done either by pressing very lightly on the blade, or by using a blunt edge. After this operation the auricle continued to beat while the ventricle stopped in diastole. The waves of contraction, starting from the auricle, beat, as it were, against the bruise without being able to get beyond it. But this lasted only a short time; after a few minutes it happened that for every three or four beats of the auricle, one succeeded in passing the obstacle and provoked a contraction in the ventricle. As time went on, the ventricular contractions became more and more frequent, until the arterial portion began to beat again at the same rate as the auricle. It was as if no injury had been done to the heart, although the groove caused by the pressure applied by the blade was still in evidence. This experiment would lead one to think that the auricle contracted automatically and the ventricle by virtue of its excitability, and one could also show that the latter has the power of accumulating subliminal stimuli and making them effective by summation, as has been demonstrated for the adult frog's heart, for muscles, and for the nervous system. In fact we may conclude that the effect of the contusion was to create a temporary depression of excitability at the auriculo-ventricular junction and so form an obstacle diminishing the efficacy of stimuli from the auricle. With the gradual passing off of this effect, the ventricle responded to an ever-decreasing sum of auricular impulses until recovery was complete and it contracts synchronously with the auricle.

This property of the contraction wave of overcoming obstacles in order to diffuse itself in the heart-tissue may also be observed if the heart is incised on both sides so as to reduce it to a scalariform band. It is then seen that the wave of contraction winds around the ends of the incisions and reaches the arterial extremity along the path we have obliged it to follow.

A similar phenomenon is observed if the heart is cut

longitudinally in narrow strips completely separated from each other. The borders are necessarily uneven because of the irregularity of the contours of the heart. The direction of these cuts is indicated in Fig. 14 by the dotted lines EF and GH. Although in this case the frequency of the rhythm is much diminished owing to the severity of the injury, the form and direction of the contraction waves do not undergo any alteration. This happens even when the auricular extremity is attached to the ventricle only by a fine thread of protoplasm which, seen under the microscope with the ordinary magnification, appears a quarter of a millimetre in thickness, but is really about $1/120$ mm. in diameter. At times, and this will be understood when the form of the heart is considered, the ends of each strip are extremely narrow and the middle portion is rather wide. Here also a thread of protoplasm from the auricle is sufficient to control the function of all the rest of the strip, since the wave of contraction regulating the intensity and frequency of the beat always arises from the narrow portion near the venous extremity of the fragment.

We must therefore subscribe to the statement that, however minute the fragments into which the embryonic heart is divided, it is never possible to alter the direction of the contraction wave. In each piece the beat travels from the part which is normally turned towards the auricle to that which is nearest the ventricle. The form and direction of the wave, as is seen, is the result of factors so deeply rooted in each fragment of the heart that not even the shock following the huge trauma inflicted by the sectioning can alter it.

But which are these factors?

If with a very sharp blade the auricular and ventricular portions are cleanly divided at the line corresponding to the auriculo-ventricular sulcus, immediately after the section, the auricle as a rule, continues to beat as before. Occasionally it stops for a few moments and then resumes its

rhythm; rarely does it show considerable, though brief, increase of frequency. In one case, for example, the auricle, after transverse section, increased the frequency of its beats from 118 to 138 per minute; on another occasion I noted a beat of 220 immediately after section. In both, however, after a short time, the rate returned to the normal of 100 to 120. The ventricle, on the other hand, immediately after section, always remained motionless in diastole; after a short time, however, it usually resumed its function, but at a rate much less than that of the auricle. Whereas arrest of the auricular portion is very rare and of short duration, that of the ventricle is constant and varies from 2 minutes to a quarter of an hour. If the transverse section is made above the auriculo-ventricular line, the phenomena just described do not occur. The ventricle remains in relation with a part of the auricle, albeit a small one, and this is enough to dominate and control the function of the arterial portion. If, on the contrary, the transverse section is made below the auriculo-ventricular groove, the stoppage is naturally confined to the fraction of the ventricle which is cut off, while that in relation with the auricle continues to beat synchronously with it. Arrest of the ventricle takes place both when a transverse section is made and when it is separated from the auricle by a longitudinal cut as indicated by the dotted line G H in Fig. 14. In this case again the ventricle continues to beat after having stopped for a certain time. But it does not always happen so; sometimes the ventricle, whether separated longitudinally or transversely, remains arrested for an indefinite time; if a stimulus is then applied, it starts beating again, sometimes until the stage of exhaustion is reached. It looks as if the heart were plunged into a sort of slumber by the injury and required a stimulus to awaken it. The same thing also occurs during the last moments of life in the heart, as was mentioned in passing *à propos* of periodical forms.

The theoretical explanation of the phenomena described

above is that the auricular portion has the property of automatic function in a much greater degree than the ventricular. But since these two parts are morphologically not entirely distinct, there is likewise no hard and fast line of separation between the points of greater or less automatism. Indeed if the heart is divided transversely into three portions at given points, *e.g.*, AB and CD of Fig. 14, the automatic phenomena of frequency, amplitude, and regularity of rhythm are maximal in the auricular portion and minimal in the bulbar extremity, while in the intermediate part they are less than in the first and greater than in the second.

If the heart is then cut into numerous small pieces, it is seen that each fragment of the auricle beats more frequently than any fragment of the ventricle. And this frequency is at its maximum in pieces belonging to the venous extremity of the auricular portion (sinus), and at its minimum in those belonging to the arterial extremity of the ventricle (bulbus).

What has been said of the frequency may be repeated with regard to the duration, inasmuch as the auricular fragments not only beat more rapidly but also function for a longer time than those belonging to the ventricular region. We must conclude that the venous part has not only greater automatism, but also shows more resistance to trauma than the ventricular part. It will be remembered that resistance to injury in a contractile organ is *cæteris paribus* in inverse ratio to its excitability, because, as we have endeavoured to show, the more excitable the organ the more harmful is the action of the trauma to which it is exposed and the deeper the alterations which it undergoes in consequence of excision and section. So that the greater resistance of the auricular portion, which is found in intact excised hearts as well as in those that have been sectioned, leads one to conclude that the ventricle is more excitable than the auricle. In favour of this hypothesis is the fact constantly observed by me that immediately after

section the auricle continues to beat at the same or at a temporarily increased rate, while the ventricle stops in general for a relatively long time. From this we infer that the ventricle feels injury much more than the auricle, for we know that while a liminal stimulus increases the frequency of the heart, a strong stimulus arrests it. In other words, the same stimulus acts feebly on the auricle and powerfully on the ventricle. We therefore conclude that the ventricle is more excitable than the auricle. I endeavoured to give a direct proof of this difference between auricular and ventricular excitability in the embryonic heart with the ordinary method of liminal faradic stimulation, using the arrangement shown in Fig. 15, while fully realising the sources of error to which it is liable. In the intact excised heart the method did not show any appreciable difference in excitability between the different parts—a result which could be foreseen, since the organ is so small, and faradic stimuli, which are liminal for the heart, but too strong to be tolerated by the hand of the operator, are readily diffused. It is clear that such conditions do not allow of the localisation of a stimulus. If instead of stimulating the intact heart the excitability of the auricular and ventricular portions is tested, after they have been separated by the guillotine, the arterial portion is discovered to be always more excitable. This is very marked at the end of the second day, when the heart still has the form of a tube of about the same diameter in its whole length, but is less obvious with the progress of development during the third day. This difference in excitability may be shown by putting the auricular extremity of the excised heart between the two electrodes and keeping the arterial extremity as far away as possible. In these conditions, using a moderate stimulus, it is observed that the distant ventricle reacts sharply, increasing its rate if it is beating or beginning to beat if it was previously at a standstill, while the auricle shows no change in its rhythm. If the excitability values are then determined separately in the auricle and in the

ventricle, putting each in turn between the electrodes, a difference is noted in favour of the ventricle. In a few cases even, the ventricular portion may be obviously excitable while the auricle scarcely responds to a strong stimulus. This difference cannot be attributed to a greater exhaustion of the auricular region, because we know that it continues to beat longer than the ventricle.

As development progresses towards the end of the third day, this difference of irritability between auricle and ventricle in the excised heart becomes gradually less and diminishes rapidly when it is near exhaustion. At this stage it may happen that the auricle shows itself the more excitable or even that it is so when the ventricle no longer responds to stimuli. This phenomenon is probably due to the greater initial excitability of the ventricle. It will be understood how an organ which is more excitable in the beginning is more affected by excision, section, and the stimulation used for measuring excitability, and therefore it will be more profoundly and rapidly exhausted by these damages. And indeed in measuring ventricular excitability at brief intervals I saw that it decreased very rapidly. Moreover an appreciable time is lost after section of the heart in arranging the different parts between the electrodes, just at the time when it would be logical to expect that the difference in favour of ventricular excitability would be at its maximum.

The explanation of the behaviour of excitability in different fragments of a heart near exhaustion has, I admit, the disquieting appearance of a *petitio principii*. But this does not trouble me. The manifestations of living beings, even the simplest, are the expression of highly complex factors. They are the resultant of multiple components which, by mutual association with one another, either reinforce themselves or interfere. It may happen that the efficacious factors annul themselves reciprocally, while others, considered negligible, by summation, make their influence prevail, and that some processes are

so bound together as to act as cause and effect on each other. The ancients, with their servid imagination and ideas, symbolised life as a serpent turned in a circle and biting its tail. Æsculapius was represented by a serpent and Hermes Trismegistus defined Divinity as a circle the centre of which is in every place and the circumference nowhere. It will therefore be understood how Ophiolatry was widely diffused in Oriental religions; and snakes are still the object of much veneration in Brahmanism.

The effects depending on the greater excitability of the ventricle lend support to the theory of cardiac automatism. Indeed in a heart cut into pieces the ventricular extremity near the sinus shows the greatest frequency, and its diminution in the different fragments in proportion to their proximity to the ventricular extremity cannot be due to variations of excitability in the different sections. This is obvious, because, if they did not depend on automatism but on excitability, if the impulse to contractions did not proceed from the inmost structure of the functional elements, but from internal physiological stimuli or from those artificially included by excision, section, division into pieces, or by faradisation, one should find that the part which beat most frequently should be the most excitable. My results show the exact contrary.

But the automaticity of cardiac function is shown, not only by the inverse ratio of frequency and duration of activity with excitability, but also by the relations, likewise inverse, between the latter and the direction of the wave of contraction. In fact, this always arises at the least excitable point, the auricle, to be propagated towards the most excitable part, the ventricle, and no stimulus, however strong, succeeds in altering its direction.

From what has been said, it follows that automatism is shown by all the segments of the embryonic heart from the end of the second and during the third day of development. It is not, however, equally distributed, as is proved by its

gradual diminution towards the arterial extremity. The contrary we can say of excitability which may be very feeble in the atrium and well marked in the arterial portion.

Besides explaining the reaction of different parts of the heart to stimulation and section, these phenomena suggest an explanation for the form and direction of the cardiac wave, a form and direction which, in the embryonic heart, are organised with such stability as to resist the most severe trauma. The auricle being the more automatic and the ventricle the more excitable, it is easily understood that the former is in the most favourable condition for emitting impulses, the latter for responding to them.

Although this functional difference is not shown morphologically with our present means of investigation, we may assume that the embryonic heart is composed of elements, or rather of groups of elements, polarised in such a manner that each possesses a maximum of excitability in the part turned towards the ventricle and a maximum of automatism in that directed towards the atrium. These elements, or groups of elements, would be the more automatic and the less excitable the nearer they are to the auricular extremity; and inversely the more excitable and the less automatic the nearer they are to the bulbus arteriosus.

This simple hypothesis will explain all the phenomena shown by our embryonic hearts; *i.e.*, the maximal automaticity and the minimal excitability at the venous extremity and the decrease in automaticity and gradual rise in excitability towards the arterial extremity, which is therefore endowed with a maximum of excitability and a minimum of automaticity. It explains how the venous extremity is best fitted to emit impulses and the arterial extremity to receive them, and why the cardiac cycle consists of a wave of contraction which is propagated from the venous to the arterial extremity and which nothing can deviate. It explains, moreover, how the ventricular

fragments, when under the influence of the auricle, obey the forcible automatic impulses emanating from it, but can also, when isolated, thanks to their automatism (which, though less than that of the auricle, is sufficient), become the seat of impulses determining their special rhythm. In other words, portions of the ventricle which ordinarily function only by virtue of their excitability making them respond to the sino-auricular impulses may become, when isolated, autonomous centres of automatic impulses.

The functional dissociations shown experimentally in the embryonic heart, which have revealed, not only the conditions freeing its peristaltic activity, but also the possibility of individual autonomy of its various segments, are not peculiar to the heart in the first stages of its ontogenetic development. They may, in fact, be discovered in this organ when its evolution is complete, as it has been made in man, where the probable factors responsible for the variations in the electrocardiogram (obtained by recording the current of action accompanying cardiac contraction) have been studied during life. Electrocardiograms in man may show the auricles beating at a normal rate, while the ventricles respond with contractions of the physiological type, as the normality of electric record shows, but much less frequent, *i.e.*, scarcely 30 contractions per minute. These infrequent beats depend on impulses arising above the ventricle in the auriculo-ventricular bundle and especially in the node of Tawara. The condition is due to an arrest of the sino-auricular impulse and is called by British investigators "complete sino-auricular block." Meanwhile the auricles contract owing to impulses derived from the sino-auricular node of Keith and Flack.⁵² This corresponds in many respects with what we saw in our embryonic heart after bruising the auriculo-ventricular line, when the frequency of ventricular beats was diminished and that of the auricular beats remained unchanged.

Anomalous behaviour of the ventricle may be induced by other conditions. When the auricular impulse is very slow and the ventricular function is therefore released from impulses of insufficient frequency, the ventricle may have its automatic rhythm, so that, although there may be no defect in auriculo-ventricular conduction, yet two independent centres for impulses may be present—the sino-auricular and the ventricular. In normal conditions, the auricular action prevails, but if its frequency drops below a certain level or if the ventricular automatism rises above that of the auricle, then the ventricle becomes independent and begins to beat with its own special rhythm. Ventricular rhythm may therefore take origin in different ways. The normal rhythm is supra-ventricular because it is derived from stimuli arising in the auricles. Anomalies are also generally of supra-ventricular origin, but due to impulses generated in the connecting bundle which, in these cases, does not transmit the excitation, but gives origin to it. It may also happen that automatic impulses arise in the ventricles themselves and carry on the office, ordinarily fulfilled by the sino-auricular node, of establishing the frequency of the ventricular beat. It is also possible to have premature ventricular contractions arising in the ventricle itself, that is, contractions not preceded by an auricular beat. This is detected by anomalies in the electrocardiogram. After each premature beat, the ventricle remains at rest, until roused by the next auricular impulse; it then responds, presenting a normal electrocardiographic tracing, because in this case the impulse has taken the usual course.* The abnormality of the electrocardiogram shows that the premature beat follows an initially abnormal path. I need hardly say that premature beats of the auricle always give rise to a ventricular contraction.

* As a matter of fact, the first sino-auricular impulse, after a premature beat, usually reaches the ventricle during the refractory period. It is therefore the second auricular impulse to which it responds.—(TRANSLATOR.)

Perchance I have dwelt too long on the subject of electrocardiographic observations, but my reason for doing so is that they prove what I was saying: namely, that the factors responsible for the results obtained on the embryo heart by bruising or section are also potentially present in the human heart fully developed and in normal surroundings. Its rhythm is normally controlled by sino-auricular automatism and, in special cases, ventricular automatism may reveal itself and become itself the source of automatic stimuli and the regulator of the rhythmic phenomena of the parts of the ventricle below it. It appears, therefore, that the functional polarity postulated for the embryonic heart of the chick is also applicable to the adult heart of man, although associated with far more complex morphological and functional conditions.

The analogy between nutation of plants, the behaviour of the embryonic heart, and the activities of the bulbo-spinal tortoise will occur spontaneously to anyone who has followed the arguments set forth in these pages. Although in a form which becomes increasingly complex and difficult to unravel, these phenomena are the outward expression of functional conditions strikingly similar. Nutations are due to changes in the turgescence of certain cells, in consequence of their nutritional activity, and produce movements of the stem which they sustain; we know, however, that these movements, so essentially and obviously automatic, may be modified, as occasion arises, by external stimuli. In the bulbo-spinal tortoise and in the embryonic heart, we have the emission of automatic impulses; in both instances, the impulses arise from one extremity—the medulla oblongata in the brain and the sino-auricular node in the cardiac tube; in both the excitability of the subjacent segments is used to release movements which take a peristaltic form on account of the successive activity of spinal metameres or of the transmission of a contractory wave to the cardiac elements. The automatism of the bulb corresponds to that of the sino-auricular node of the heart

and the excitability of the spinal segments recalls that of the preponderatingly excitable elements of the ventricle. The upper segments of the medulla and the sino-auricular node work with their own periodicity which express the metabolic activity of the cells of which they consist; the spinal cord and the ventricle respond passively to these stimuli, keeping pace as required by the upper automatic regions.

The comparison is still more apt if we investigate what happens during embryonic development of spinal function, comparing it with the facts observed in the ontogenetic development of cardiac function. I will refer to investigations carried out in my laboratory when I was at Florence by my assistant, Prof. Gino Cesana.⁵³ His experiments, performed on the white rat, *Mus rattus*, *v. albinus*, during foetal life, in the new-born and in the adult, showed, among other interesting facts, that the bulbo-spinal tract during ontogenetic development becomes gradually more excitable and that its automatic capacity gradually diminishes, precisely as was observed in studying the embryonic development of cardiac function.

Another fact, already mentioned, emerges even more clearly from the foregoing observations and experiments; not only are the most fundamental functions of life entrusted to organs that, although excitable, are fundamentally automatic, but automatism is the primordial form of motor mechanism. It is only later that this becomes excitable. Thus in the different stages of embryonic life, as in the different species, automatism prevails in the lower forms and excitability is dominant in the higher. The former advance blindly through life, moved by internal impulses whose uniform action is hardly capable of adaptation to fundamental modifications in the environment. Nevertheless, their continuity of life is sufficiently guaranteed by an organic resistance which is a function of their low excitability. This function, however, lends itself only to slow reactions and adaptations of little variety and importance. The higher

forms, owing to their excitability which increases as we ascend the animal scale, can react intensely, rapidly, and adequately to a variety of stimuli, even when scarcely perceptible; but this selfsame excitability makes them extremely delicate. In order then to resist the ceaseless demolishing actions of the environment and to meet the innumerable and varied requirements of their delicate structure, they must be consciously or unconsciously armed by means of agile, powerful, and varied powers of response and complicated physical, chemical, and structural adaptations. This is most obvious in man. His life is a continual struggle; it may be a source of great pain, but suffering acts as an effective spur and it brings comfort by the thought of the advantages gained for himself and for his fellow-creatures.

We have seen how even a humble tortoise may demonstrate experimentally the daily lesson of life, *i.e.*, that the physiological causes of psychic phenomena are mainly the result of inhibitory acts, especially when they provide for the defence of the individual and of the species. Do we not see every day that the superiority of a being depends above all on his dominion over himself, on the inhibition of those atavistic impulses which too often reduce man to the level of the brute? And does not education consist chiefly in the exercise of inhibitory powers?

In reality, as has been said, physiology should not be considered only as a natural, but also, I venture to say, as a moral science. For the intimate collaboration of the tissues in defence of the whole of the organism and especially of those parts which make of it a reacting and sentient being, offers a wonderful example which we should faithfully follow for the discipline and direction of our conscious life. Take, for example, the behaviour of all the tissues during a fast. They pour into the blood-stream their reserves and finally the products of their own destruction to guarantee as long as possible the functional integrity of the nervous centres which are the essential seat of the

most important co-ordinating actions, the foundation of the greater part of unconscious and of all conscious acts.

And in truth, the nerve centres are the most fundamental character of a living individual and in a special way of man. No organ is as complex as the central nervous system and especially the brain. Particular idiosyncrasies show us individual differences in the tissues and body fluids, in the endocrine constitution, and in other functional somatic conditions, hereditary and acquired, of the various organs. But these differences are never so marked as are those between individual nerve centres. Nor can we reject that differences in organs are, at least partially, the more or less remote results of differences between their central innervations. Nervous centres of individuals are also differentiated, and sometimes above all by accidental events which they have experienced in the past. Mnemonic images are thus more or less deeply fixed in the brain as well as associative relations, paths of conduction and special aptitude for reception and projection. These are among the principal factors of an active and sentient personality. Indubitably there are between the brain and the other organs such innumerable relations, that each reflects the other; but no organ is so plastic as the brain, none has so different a history in each individual and therefore none has attained so great a diversity of impressions received, of deeds accomplished, of powers acquired; no organ, in fine, has so much individuality. Thus the energies, whatever they may be, which move the different tissues of the organism bring about reactions that are in general constant and uniform in organs concerned with vegetative life, while the brain reacts in a manner which is above all individual just because its past has specially differentiated it. Its reactions therefore may be sometimes appropriate and in other cases appear contrary to the most obvious requirements of individual and collective defence.

History teaches us that the most successful nations are those in whom the impulses of individuals are subjected to

the needs of the whole collectivity to which they belong. Misfortune, on the other hand, befalls nations in which predominate the selfish influences of individual intolerance and strife.

May human consciousness, better guided by experience and made more sensitive to the suffering of others, model itself on the unconscious functions, and with unceasing and disciplined activities, gaze ever upward to the summit of its ideals, to the sacrifice of the individual for the triumph of humanity which aspires to be raised to the height of goodness, truth and beauty. May it learn from the dying Faust, tragic symbol of humanity, the words interpreting his conflicts of thought, the rebellion of his senses and the work of redemption which are for him the end of wisdom :

Freedom alone he earns as well as life,
Who day by day must conquer them anew.

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